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ETHICAL CHALLENGES RELATING TO PROVISION OF SUSTAINABLE RENAL CARE IN RESOURCE LIMITED SETTINGS - FOCUS ON SUB-SAHARAN AFRICA

INAUGURAL-DISSERTATION

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ABSTRACT

Kidney disease is increasingly being recognized as a public health problem, not only because large numbers of patients are affected, but also because of the diagnostic and therapeutic challenges associated with its management, especially in low resource settings, where conflicts between financing, equity and social values frequently arise. When kidneys fail, either acutely or chronically, dialysis represents an immediate life-saving therapy. Dialysis is technically available in most countries, but is time, labor and resource intensive, which limits access largely to those who can afford to pay when not covered through universal health coverage or health insurance. Access to dialysis is therefore highly inequitable across country income groups globally and within countries. Dialysis poses ethical challenges at many levels in low-resource settings. Policy makers must consider whether to provide dialysis at all or leave it to market forces. If dialysis is to be provided, who, where and how to dialyze safely and equitably are necessary questions to consider. When these questions are not addressed transparently at a policy level, clinicians and families must face complex decisions about whether to start dialysis or not at the bedside.

Policy-making requires evidence. Based on broad inequities in access to dialysis and the potential consequences for individuals and families, health care workers, the health system and society, this PhD begins with an epidemiologic description of outcomes in patients requiring dialysis in sub-Saharan Africa and consequent moral distress experienced by nephrologists at the bedside, investigates overarching strategies to reduce the global burden of kidney disease, and focuses on the ethical implications of priority setting and policy making regarding provision of dialysis in sub-Saharan Africa.

In Chapter 1, the results of two systematic reviews on access to dialysis and outcomes in patients with both acute and end-stage kidney failure in sub-Saharan Africa are presented. Both studies confirm poor access to care and high mortality even when access to care is possible, largely because of reliance on out-of-pocket payments in the region. In Chapter 2, results of a survey of nephrologists regarding management of patients who require dialysis in sub-Saharan Africa show a high level of moral distress, largely driven by unaffordability of necessary diagnostics and therapeutics. Given that kidney disease would be preventable through improvements in living standards and some basic public health measures, and treatable with early diagnosis and access to appropriate medicines, broad strategies to achieve these at a

public health and a policy level are discussed in Chapter 3. The importance of policy development governing provision of, and access to, dialysis is discussed in Chapter 4, together with an ethical analysis of potential policy approaches. Policy development should be inclusive, transparent and responsive. Ethical guidance regarding potential steps to strengthen and support the policy-making process are suggested.

The ultimate goal of the work presented here is to generate data to inform policy-making and to empower clinicians, patients and families to raise and articulate ethical concerns regarding care for kidney disease. The need for transparent and fair priority setting in low resource settings must be clearly communicated. Meaningful engagement with all stakeholders in the policy-development process is required to develop a holistic system-wide approach to sustainably and equitably tackle the rising global burden of kidney disease.

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ABBREVIATIONS

A4R	Accountability for Reasonableness
AKI	Acute kidney injury
CHE	Catastrophic Health Expenditure
CKD	Chronic kidney disease
ESKD	End-stage kidney disease
GBD	Global burden of disease
GDP	Gross domestic product
HD	Haemodialysis
HDI	Human development index
HIC	High income country
IR	Implementation research
LMIC	Low and middle income countries
NCD	Non communicable disease
NHI	National health insurance
OOP	Out-of-pocket
PD	Peritoneal dialysis
QALY	Quality adjusted life-year
RRT	Renal replacement therapy
SDG	Sustainable development goals
SSA	Sub-Saharan Africa
USRDS	United States Renal Data System
WHO	World Health Organization
YLL	Years of life lost

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INTRODUCTION

Kidney failure disproportionately affects the poor, its treatment is predominantly accessible to the rich. This inescapable paradox has been the driving force underlying this PhD. The overarching goals have been to understand more about the global burden of kidney disease, with an emphasis on sub-Saharan Africa (SSA), and to consider the ethical challenges associated with the management of kidney disease in lower resource settings. Much has been learned about the global burden of kidney diseases in the past 4 years since the initiation of this PhD, which highlights the relevance of the topic. Some of this knowledge has been contributed by the work done during this PhD. For completeness, rather than adhering to the chronology of knowledge development in the field, the latest data regarding the global distribution of kidney disease and global inequities in access to care are summarized here in the introduction, as rationale for the work that follows.

The clinical spectrum of kidney disease

It has recently been estimated that around 850 million people world-wide are affected by some form of kidney disease.[2] This figure covers a broad spectrum of individuals. Around 13 million people per year are estimated to develop acute kidney injury (AKI). AKI reflects a sudden worsening of kidney function in response to an acute insult or event (e.g. medication side-effect, severe infection, heart failure), which can recover under favorable conditions. In around 11% of cases AKI is severe enough to cause acute kidney failure, meaning that short-term dialysis may be required to replace the kidney function until it recovers and to keep the patient alive. Dialysis in such cases is usually required for days or weeks. Depending on the severity of the AKI, the kidney function may return back to baseline or there may be some permanent loss of kidney function, which then becomes chronic kidney disease (CKD). CKD reflects permanent loss of kidney function to varying degrees, from mild to end-stage. CKD results from many different causes, the most frequent of which are diabetes and hypertension.

According to the Global Burden of Diseases (GBD) study, 750 million people were living with CKD in 2016.[3] When mild, CKD may only manifest with abnormal leakage of protein into the urine (proteinuria, affects 475 million people[3]), which if controlled may remain stable for many years.

Proteinuria is however a major risk factor for cardiovascular disease, the world's biggest killer. Depending on the degree of damage, and timeliness of appropriate diagnosis and care, CKD may progress over time as the remaining functional kidney tissue overworks and essentially consumes itself to maintain a steady state.

Once kidney function deteriorates beyond a certain point (around 30% of normal kidney function, 13 million people[3]), patients begin to feel unwell and once kidney function reaches around 10-15% of normal kidney function (a further 10 million people[3]) many patients become symptomatic enough to require renal replacement therapy (RRT) in the form of dialysis or transplantation, i.e. they reach end-stage kidney disease (ESKD). Transplantation (0.7 million people in 2016[3]) is the ideal form of RRT as this provides optimal quality of life, survival and is most cost-effective. Transplantation however requires robust health care infrastructure, appropriate legislation, complex specialist follow-up and life-long access to immunosuppressive medication. Dialysis (received by 3 million people in 2016[3]) may be provided in 2 major forms. Hemodialysis (HD) requires a machine to "clean" the blood generally for 4 hours 3 times a week, which can be done in a dialysis center or at home by trained patients. Blood is circulated from the patient to the machine and back via a large-bore venous catheter placed in the neck or a surgically placed arterio-venous connection in the patient's arm. Peritoneal dialysis (PD) involves a catheter being placed in the abdominal peritoneal cavity through which 2 liters of dialysis fluid is exchanged 4 times a day either manually by the patient or by a machine during the night. The placement of the vascular or peritoneal access for dialysis requires trained operators, sterile conditions and technical supplies. HD requires functioning machines, stable electricity and a reliable water supply, as well as tubing, filters and other supplies, mostly new for each treatment. PD requires new dialysate fluid bags and tubing for each exchange. Training of dialysis staff and patients is required for both HD and PD. The costs of dialysis and transplantation are variable, in some settings driven largely by staff costs, in others by supply costs. Transplantation costs around USD 10 000 to USD 20 000 per patient per year (excluding surgical and hospitalization costs in the first year which are high), whereas annual costs for HD and PD range on average from round USD 4000 in some low income countries to over USD 70 000 per patient in high income countries.[4,5] The ratio of costs between HD and PD varies across countries despite PD in theory being cheaper as it requires much less infrastructure.[6] Costs in SSA are known to be inflated by customs, "fees" and middle-men.[7-9] Both forms of dialysis

replace around 20% of kidney function and therefore patients remain chronically ill, have high pill burdens and experience frequent complications necessitating repeated procedures and hospitalizations. A significant proportion of both AKI and CKD could be successfully prevented through public heath measures.[10]

The public health relevance of kidney disease

Kidney disease and its risk factors cross the spectrum of the human condition: from poverty to affluence, from under- to over-nutrition, from fetal life to old age, from agricultural to industrialized societies, from traditional to modern medicine, from infections to non-communicable diseases (NCDs), from inherited to preventable diseases, and from acute and reversible to chronic and irreversible illnesses.[11] Its management extends from healthy lifestyle choices and cheap generic medications to highly expensive therapies such as dialysis and transplantation. Kidney disease prevalence and access to care are also impacted by ethnicity, gender, religion, occupation, geography and the legacy of colonialism.[11] In the current global context, where leaders are failing to tackle many of the social determinants of health, discrimination and disparities remain high, working conditions remain unsafe, pollution is increasing, and due to climate change, natural disasters and environmental threats are becoming more frequent. Consequently, the risk of kidney disease, impacted by all of these factors, is also increasing.[10,11] The global burden of kidney disease has however been relatively neglected despite the recent acknowledgement that NCDs as a group are now the major cause of global mortality.[11,12]

The World Health Organization (WHO)'s Global Action Plan for NCDs has focused the world's attention on 4 NCDs (heart disease, cancer, respiratory disease and diabetes), with a recent addition of mental health, chosen because they account for the majority of *known* NCD deaths.[12,13] Although positive, in that the burdens of these diseases have begun to decline, many other NCDs are being "left behind" as countries focus on meeting these high profile disease targets. It is therefore not surprising that the global burden of kidney disease is continuing to rise while many other disease burdens are beginning to stabilize or improve.[14,15] Based on increasing awareness and diagnosis over the past few years, as well as population aging, it is

projected that by 2040 CKD will become the 5th most common global cause of years of life lost (YLL).[16]

Global inequities in access to diagnosis and care for kidney disease

One reason for the under-recognition of the kidney disease burden thus far may be the necessity of laboratory testing for diagnosis which is not universally accessible, and consequently awareness is low.[11] Also, the late symptoms of kidney disease are similar to those of heart failure, which are therefore difficult to discern on verbal autopsies. As far as possible, the global burden of CKD is tracked by the GBD study, and renal registries in several countries track the incidence and prevalence of ESKD. Around 2.4 million people are known to die annually directly from CKD or from it's contribution to cardiovascular deaths.[17] The burden of AKI is however unknown, but mortality is estimated around 1.7 million per year.[18] In high income countries CKD, and to some extent AKI, tend to be diseases of aging. This may explain why until now, given that most data has been available from higher income settings, the YLLs as a consequence of CKD have been relatively lower than those of other diseases, especially when the focus has been on "premature" NCD deaths, i.e. those occurring between ages 30 and 70 years.[19] In low and middle income countries (LMICs), however, both AKI and CKD affect a younger demographic, predominantly in the 20 – 50 year age group, i.e. the economically active population.[20] As more kidney disease deaths are counted in these regions, the YLL from CKD and AKI will increase. Regardless of age, however, even a death from CKD over age 70 may be too early when it results from lack of access to care and therefore equity demands attention to care across the age spectrum.

Overall it is estimated that 10% of the world's population has some form of CKD and this prevalence seems relatively consistent across countries and regions.[3,21] Despite this, the ranking of CKD as a cause of death is variable across country income categories as highlighted in Table 1.[22] In higher income settings, the proportion of CKD contributing to YLL has not changed much over the past decades, likely because of fairly consistent access to diagnosis and treatment. In lower income settings, in contrast, CKD ranking remains low, likely because of persistent predominance of infectious causes of death, as well as missing data due to lack of access to diagnosis. The proportional increase in CKD rank is however the largest in these countries, potentially reflecting increasing access to diagnosis and better control of infections.

Table 1: Ranking of chronic kidney disease as a causes of years of life lost (YLL)

	1990	2006	2016	Change in rank 1990-2016
High income countries	17	14	13	4
High-middle income countries	22	18	17	5
Middle-income countries	19	15	10	9
Low-middle income countries	25	21	18	7
Low income countries	37	32	26	11

Data compiled from [22]

CKD appears to be the most significant public health problem in middle income settings, especially in Central America where in some countries it even ranks among the top 3 causes of death (Mexico, Nicaragua, El Salvador, Costa Rica).[22] These observations may reflect a transition status in middle-income countries where access to diagnosis of kidney disease has markedly improved over the past decades, but universal access to treatment is still lagging behind.

Globally CKD is more prevalent among ethnic minorities and disadvantaged groups, even in high income settings, and is generally more common and progressed more rapidly in people of African origin.[20,23] Data from SSA is not comprehensive, but the prevalence of CKD is at least as high if not higher than in other world regions, based on the high prevalence of hypertension and infections, possible genetic susceptibility, and the rising prevalences of obesity and diabetes.[24,25]

Global inequities in access to renal replacement therapy

Currently over 3.0 million people globally live on dialysis or with a kidney transplant, a number which is projected to rise to 5.4 million by 2030.[1] Over 90% of people receiving RRT currently live in high or upper middle income countries, but the largest growth is anticipated in Asia and Africa (Figures 1 and 2).[1]

Figure 1. Global distribution of patients receiving RRT* by country income group (2010)
(Reprinted with permission from [1])

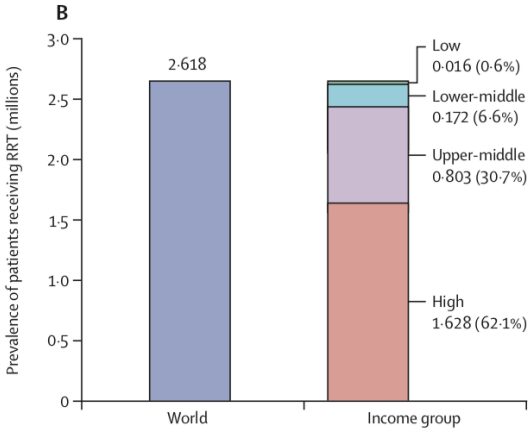
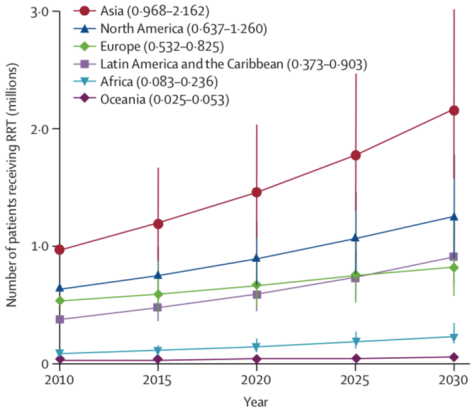


Figure 2. Projected increase in patients receiving RRT* 2030.
(Reprinted with permission from [1])



*RRT reflects dialysis and transplantation in these figures.

It has been estimated that between 2.3 and 7.1 million people with ESKD may have died prematurely in 2010 because they could not access dialysis or transplantation.[1] Specifically, based on the known risk factor prevalences, it has been similarly estimated by other authors[26] that only 1.5 % of people with ESKD resulting from of hypertension or diabetes (the most common global risk factors for ESKD) likely gain access to treatment in SSA, as opposed to almost 100% in high income settings. These projections, although only estimates, highlight the glaring regional inequities in access to RRT across the globe. Similar numbers for AKI are not available, but likely many of the estimated 1.7 million deaths result from lack of access to dialysis.[27]

Challenges in access to renal replacement therapy in sub-Saharan Africa

Fewer than 1% of the world's dialysis population live in SSA which is home to 16% of the world's population, a statistic that reflects lack of diagnosis and poor access to care rather than a low prevalence.[28] Data from the latest report on international comparisons of ESKD from the United States Renal Data System (USRDS), compiled from 62 reporting countries, is outlined in Table 2. The only data from SSA included in this database is from South Africa as it is the only country with an ESKD registry. South Africa was consistently ranked among the lowest countries globally for all rates reported. True ESKD incidence rates in SSA are unknown as it is not known how

many people who develop ESKD remain undiagnosed or how many among those who are diagnosed gain access to care.

Given the lack of formal epidemiology, recent estimates based on surveys of nephrologists from 36 of 49 sub-Saharan African countries report prevalent dialysis rates ranging from zero in 2 countries (Central African Republic, Sierra Leone) and less than 10 per million population (pmp) in 14 countries, to over 150 pmp in 6 countries (Gabon, Mauritania, Mauritius, Seychelles, South Africa, Sudan and Swaziland).[29]. In contrast, prevalence rates from North Africa range from 300 pmp in Algeria to 734 pmp in Tunisia.[30] The inequities between SSA and the rest of the world are therefore significant, as are the inequities within SSA itself.

Table 2: USRDS international rates of treatment for End Stage Kidney Disease (2016)

	Ranking	Country	Rate per million population (PMP)
Incidence, treated ESKD	Highest	Taiwan	493
	Median	-	140
	Lowest	South Africa	22
Prevalence, treated ESKD	Highest	Taiwan	3392
	Median	-	930
	2nd lowest	South Africa	181
	Lowest	Bangladesh	117
Prevalence, dialysis alone	Highest	Taiwan	3251
	Median	-	528
	4th lowest	South Africa	156
	Lowest	Bangladesh	113
Prevalence, living with a functioning transplant	Highest	Portugal	693
	Median	-	344
	Lowest	South Africa	25

Data compiled from [31]

As shown in Figure 3 in general the availability of RRT is a function of a country's gross domestic product (GDP), although the association tends to be lost in high-income countries where the prevalence of ESKD likely reflects the true disease prevalence rather than being dependent on access to treatment.[32] In some cases, countries with lower resources have found ways to extend universal access to RRT (Figure 4).[33] Some sub-Saharan African countries also have a relatively low GDP but a relatively high prevalence of treated ESKD. In these settings, where the human development index (HDI, a composite score reflecting life expectancy, education and per capita

income) [34] is also low, public financing for ESKD could be questioned given possible higher priority issues (the importance of priority setting is discussed below).

Figure 3. Prevalence of treated End Stage Kidney Disease (pmp) relative to Gross Domestic Product (GDP) per capita, 2015

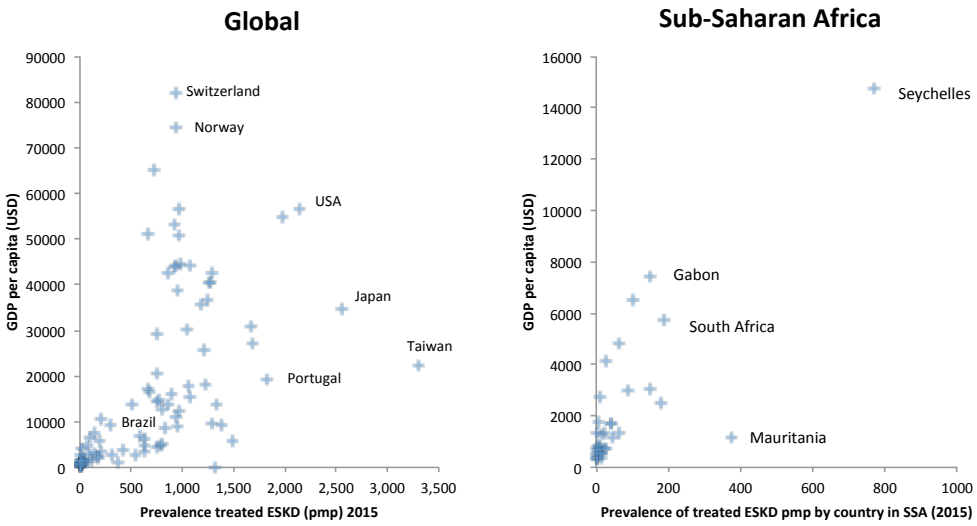
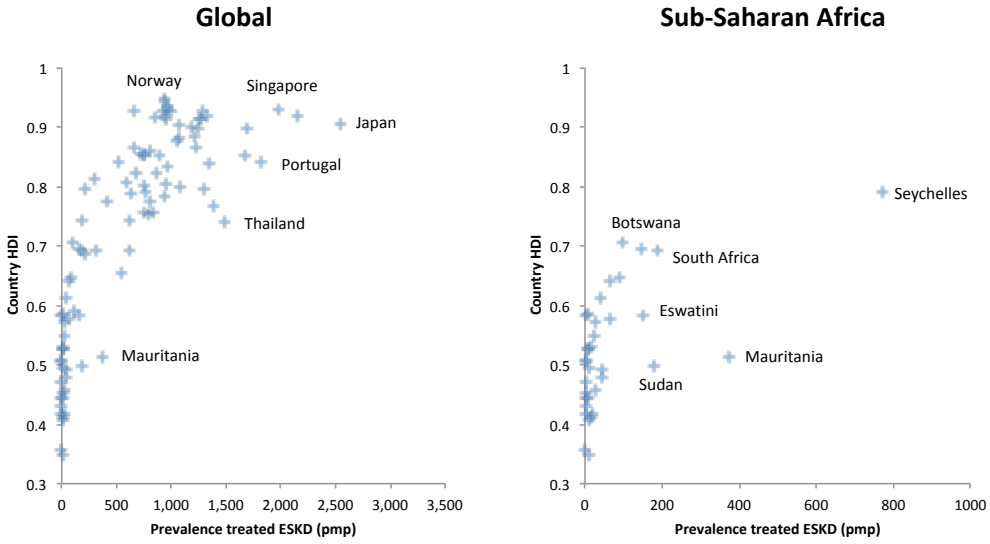


Figure 4. Prevalence treated End Stage Kidney Disease (pmp) relative to country Human Development Index (HDI), 2015



Figures 3 and 4 were generated from [29,31,35,36]. Note different x and y axis scales in Figure 3 and x axis scales in Figure 4.

Global reimbursement for dialysis (excluding out-of-pocket payments) amounts to around 57 billion US dollars, 80% of which is spent in high-income, 17% in middle-income, and 3% in low-income countries.[32] In most countries where dialysis is universally available this is funded through governments utilizing varying financing schemes, as the annual cost of dialysis is unaffordable for individuals.[37] In these countries, on average 2-4% of national healthcare budgets is directed to ESKD care, which affects around 0.15% of the population.[38] This disproportionate health expenditure has evolved as consistent with prevailing social values of not abandoning patients to almost certain death without RRT.[39-41] In such settings the current ethical challenge often concerns not whether people can be kept alive with RRT, but at times, whether they should be, especially when quality of life becomes extremely poor.[42]

In many lower income settings, and throughout most of SSA, access to RRT is not universal and is largely dependent on a patient's ability to pay, mostly out-of-pocket in private centres.[43-45] Even when some attempt at government funding is made, dialysis facilities in SSA are located in large urban centers, are fraught with technical and infrastructural challenges and are not enough to meet the clinical need.[46,47] The percentage of the health budget allocated to the few patients who may access government-supported dialysis is therefore highly disproportionate.[48] Transplantation is rarely available. Opportunity costs for the health system are therefore likely extremely high, however the individual costs in terms of money and/or life lost when coverage is absent are also catastrophic [a].[48] The predominant ethical challenges under these circumstances therefore concern whether and how patients who should be dialyzed can be dialyzed; if dialysis is provided, who should pay and how much, and whether this involves quality compromises; if patients cannot be dialyzed, what alternative support is in place? Far less commonly, the question of whether a patient who technically can be dialyzed should be dialyzed (e.g. in the case of severe brain injury) also arises.

Over the past few decades, several single-center descriptive studies have highlighted the challenges associated with the management of kidney disease in SSA. These studies describe small patient numbers, suboptimal access to dialysis treatment and poor outcomes for both AKI

[a] Catastrophic health expenditure (CHE) is defined as an out-of-pocket health care expense amounting to over 10% of overall household income or 40% of non-food household expenditures.

and ESKD. An analysis of factors which limited access to dialysis among children in a single specialty unit in Nigeria illustrates the multiple challenges faced daily in SSA.[47] Despite 33 of 51 families stating that they could afford to initiate dialysis for their children, only 6 children finally received dialysis.[47] Instead, most children who required it were not dialyzed because of lack of, or non-functioning dialysis equipment (22 children), staff shortages (3 children), or staff hesitance to dialyze for fear the family could not afford it (3 children).[47] Surveys and review articles have emphasized the projected unmet need for RRT in the region as discussed above, and have highlighted the lack of trained staff.[28,49,50] Such "anecdotal" evidence may not be very convincing to policy makers and other stakeholders however. Thus far, in many countries, policy makers have declined to develop explicit policies regarding provision of, and access to, dialysis. Under such circumstances, given that at least private units are present in almost all countries[51], some patients do gain access to dialysis. In some cases this is life saving, but very likely more often than not it postpones death by days or weeks. Families of poor patients with ESKD (and likely also those with AKI requiring dialysis) go from being "worse off", and arguably deserving of state support in this basis, to being even worse off after having experienced catastrophic health expenditure (CHE) and having lost a loved one, often the breadwinner.

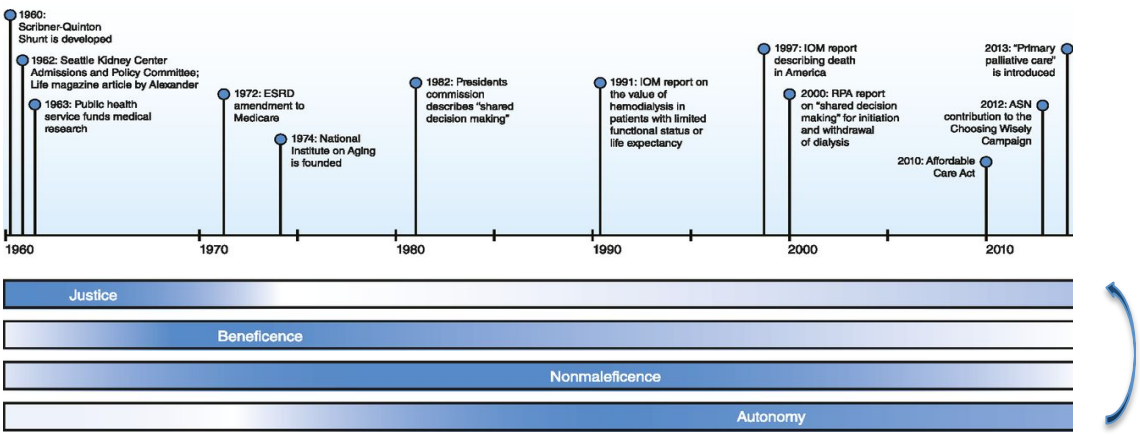
A commentary regarding "Equity and economics of kidney disease in SSA"[48], published as part of the Lancet Series on CKD in 2013, raised vehement debate from senior nephrologists both within and outside of Africa, about whether countries in SSA should consider providing dialysis, given the high costs, poor infrastructure, and the "few" patients involved (personal communication). Regardless of personal opinions, rigorous data has been lacking, dialysis is available in SSA, and its consequences in terms of CHE and life or death for individuals, and stress and opportunity costs for health systems cannot continue to be ignored. How best to tackle this multifaceted problem is unclear.

Access to dialysis – nephrology as a pioneer of biomedical ethics

Many papers and book chapters on resource allocation for high-cost medical therapies begin with a description of the dilemmas surrounding rationing of dialysis in the United States (US), which is heralded by some as the debate that brought biomedical ethics into the mainstream (Figure 5).[52,53]

The US was the first country to provide chronic dialysis which became available to all those who required it in 1972. Prior to this, once chronic dialysis became a technical reality in the early 1960s, the overriding ethical challenge related to the principle of justice, as the existing scarce resources could not meet the clinical need. Initially access was only available to those who could pay, but given the unfairness of this, a "Life or Death Committee" was struck to take "objective" decisions on who should receive dialysis.[54] The fact that these decisions were based on a patient's perceived "social worth" led to a public outcry. Subsequently, based on the rule of rescue and a significant underestimation of the projected need, all ESKD patients became eligible for dialysis under the Social Security Act Amendment.[39,55] This decision also set a benchmark for quality adjusted life-year (QALY) thresholds, which are used as indicators of society's "willingness to pay" for a year of life, and established a limit against which other high-cost treatments have been measured.[56,57]

Figure 5: The evolution of access to dialysis and the progressive ethical challenges in the United States. [Reproduced with permission from[55]]



Following this utilitarian approach, an individual's resources no longer determined access to care in the US and individual patient autonomy became the deciding factor (Figure 5). The understanding initially had been that the small number of patients requiring dialysis would be "rehabilitated" by this treatment and flourish. Even early on however it was realized that many severely ill patients were surviving, but not thriving on dialysis, raising the question of which patients were "appropriate" for dialysis.[58] Indeed, the original pioneer of chronic dialysis, Dr.

Belding Scribner, stated there should instead be a "de-selection committee".[58] The ethical challenges associated with dialysis therefore had shifted from the macro- and meso-scales to the micro-scale of better understanding the benefit (beneficence) and potential harms (nonmaleficence) of dialysis for the individual at the bedside.[55] Indeed it is now recognized that certain patient groups, especially the frail and elderly may actually do better without dialysis and with supportive care.[59,60] The multiple clinical ethical challenges related to dialysis on the micro scale have recently been expertly reviewed elsewhere.[61]

Throughout the evolution of dialysis, as technical and access barriers were progressively overcome, the demand and costs have grown far more than initially anticipated. Before dialysis became routinely available an element of therapeutic nihilism prevailed regarding kidney disease. The disease burden was therefore markedly underestimated. Given that now over 500 000 patients in the US receive dialysis, representing < 1% of the Medicare population but consuming 7% of the Medicare budget[62], questions of sustainability are beginning to arise, bringing the ethical questions back to those around justice (Figure 5).[55]

The diverse ethical challenges on the macro-, meso- and micro-scales being faced currently by lower income countries regarding access to dialysis are therefore not new, and it is likely that this ethical cycle is being replayed in many settings. Where universal coverage for dialysis is absent, however, the predominant questions on the macro- and meso- scale concern justice and opportunity costs, and on the micro-scale, concern potential benefit and likely harm given that few can access treatment, and among those who do, many cannot sustain long term benefit and may leave their families worse off. How policy makers should approach these conundrums is unclear given their roles as chaperones of the health system as a whole, but also their obligations to help individuals to achieve their highest attainable state of well-being.

The work presented in this PhD represents my own journey from attempting to deliver compassionate and appropriate care at the bedside under resource limited conditions, which raises many moral questions, to understanding ethics as a means to unpack and communicate effectively about some of these dilemmas, to learning about priority setting as a rational means to try to approach these dilemmas, and to the World Health Organization where the pursuit of

the ideals of “health for all” and universal health coverage (UHC) may one day translate into access to care for all patients with kidney disease everywhere.

RESEARCH OBJECTIVES

The public health importance of kidney disease does not only lie in the large numbers of patients affected, but also in the potential conflicts between financing, equity and social values related to the diagnostic and therapeutic challenges associated with its management. Dialysis is an immediate life-saving therapy, which is fairly easily technically accessible, but is time, labor and resource intensive. In the case of patients with AKI it is hoped that dialysis may only be required for days to weeks and that kidney function would recover enough that dialysis could be stopped, resulting in a short-term dependence on this high-cost therapy. A prevailing presumption in the nephrology community is that dialysis for AKI should be accessible to all as a “human right”, but little discussion has been generated on how this can or should be operationalized.[27,63]

In contrast, for patients with ESKD, unless a more cost-effective kidney transplant is possible, dialysis is required for the remaining years of life at significant continuous expense. It has been suggested that state provision of dialysis is an “unacceptable” health care trade-off given the opportunity costs in countries without UHC.[64] Dialysis therefore poses many ethical challenges for individuals and policy makers in low-resource settings, not the least of which are what price to put on a life, and how and whether to govern access to such expensive care. Policy makers must consider whether to provide dialysis at all or leave it to (private) market forces, whether to implement dialysis in limited vertical programmes, or to embed it in more horizontal kidney and NCD management programmes. If dialysis is to be provided, who and how to dialyze, what quality standards should be acceptable, and where facilities should be located to maximize access, safety, effectiveness and equity are necessary questions to consider. When policy makers fail to address such issues, many of the decisions devolve to the clinicians and families at the bedside of imminently dying patients, which can be highly distressing to all.

Transplantation is clinically much more complex than dialysis and currently can only address the needs of a very small proportion of patients who develop ESKD in SSA. Transplantation also

extends beyond kidney transplantation alone and is fraught with its own additional layers of ethical challenges. As such, the work described in this PhD focuses primarily on ethical challenges associated with dialysis, the discussion of which is likely to be more immediately generalizable. The topic of access to and resource allocation required for transplantation in low-income settings will be addressed in future work.

Policy-making requires evidence, both to illustrate that a problem is indeed a problem, and to generate ideas for potential strategies to address the problem in a just and transparent manner. Based on the broad inequities in access to dialysis for AKI and ESKD described above in SSA and across the globe, and the potential consequences of individuals and families, health care workers, the health system and society, the objectives of this PhD begin with an epidemiologic description of outcomes of patients requiring RRT in SSA and experiences of nephrologists managing patients with kidney disease under current circumstances, proceed to outline some overarching strategies to reduce the global burden of kidney disease, and finally focus on the ethical implications of policy making regarding provision of RRT in SSA. The presentation of the papers in each chapter is followed by a brief interpretation of the findings.

In **Chapter 1** the results of two systematic reviews on access to RRT and outcomes in patients with both AKI (41 studies) and ESKD (68 studies) in SSA are reported (*Paper 1 and Paper 2*). Both studies confirm poor access to care and high mortality despite access to care, especially for patients with newly diagnosed ESKD, most likely because of large reliance on out-of-pocket payments in the region.

In **Chapter 2** results from a survey of 39 nephrologists from 15 countries across SSA are reported regarding challenges faced at the bedside in management of patients with AKI or ESKD who require RRT. The results illustrate a high level of moral distress among the nephrologists, largely driven by unaffordability of necessary diagnostics and therapeutics (*Presentation 1*).

Access to dialysis for those who need it is therefore a common clinical dilemma for patients and health care workers in SSA. Given the expense and health systems components required to deliver equitable and sustainable RRT in SSA, there is no quick fix to this problem. Prevention of kidney disease and thereby the need for RRT would appear the most cost-effective long-term

solution. In **Chapter 3** strategies for prevention of kidney disease are outlined from a clinical and a system-wide perspective (*Paper 3 and Paper 4*), many of which are implementable solutions which have potential benefits in reducing inequities beyond kidney disease alone.

Building on the findings of the systematic reviews and the nephrologist survey outlined in Chapters 1 and 2, in **Chapter 4**, the ethical challenges associated with provision of dialysis in resource-limited settings are reviewed (*Paper 5*). Potential policy approaches to kidney disease are discussed regarding their impact on equity and justice in terms of access to dialysis, efficiency and opportunity costs. A framework of ethics developed for implementation research is described which may be useful to guide transparent and equitable decision-making and planning regarding implementation of expensive heath care interventions (*Paper 6*).

It is hoped that the work presented here may be useful to inform regional policy makers and advocacy activities about the realities faced by patients, families and health care workers confronted with kidney disease in SSA. Ultimately the goal is raise to awareness of the need for transparent and fair priority setting around access to high cost, but life-saving, interventions such as dialysis in low resource settings and to catalyze engagement with all stakeholders to develop a holistic system-wide approach to sustainably tackle the rising global burden of kidney disease.

CHAPTER 1. Access to renal replacement therapy and outcomes in patients with both acute (AKI) and end-stage kidney failure (ESKD) in SSA

Given the many presumptions about access to dialysis and outcomes in SSA, the lack of large rigorous studies, and the relative lack of policies regarding kidney disease and dialysis, two systematic reviews were conducted to consolidate published literature on the topic (*Paper 1 and Paper 2*) and objectively describe the clinical realities on the ground. Outcomes captured included access to dialysis when required, mortality, duration of follow-up, access to transplantation, dialysis dose, availability of associated medications and dialysis access use. This chapter builds upon preliminary work conducted as part of my MSc thesis at the London School of Hygiene and Tropical Medicine in 2013. A group of leading sub-Saharan nephrologists were subsequently invited as co-investigators to extend the search, to perform a rigorous collaborative systematic review according to PRISMA guidelines, and to ensure representativeness and coherence of the findings with their experiences. These papers were published in high impact journals, both accompanied by editorials and *Paper 2* was also accompanied by a commentary, all indicating the topical relevance to global health.

PAPER 1

OUTCOMES OF ACUTE KIDNEY INJURY IN CHILDREN AND ADULTS IN SUB-SAHARAN AFRICA: A SYSTEMATIC REVIEW

Wasiu A Olowu, Abdou Niang, Charlotte Osafo, Gloria Ashuntantang, Fatiu A Arogundade, John Porter, Saraladevi Naicker, Valerie A Luyckx

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Outcomes of acute kidney injury in children and adults in sub-Saharan Africa: a systematic review

Wasiu A Olowu, Abdou Niang*, Charlotte Osafo, Gloria Ashuntantang, Fatiu A Arogundade, John Porter, Saraladevi Naicker, Valerie A Luyckx*

Summary

Background Access to diagnosis and dialysis for acute kidney injury can be life-saving, but can be prohibitively expensive in low-income settings. The burden of acute kidney injury in sub-Saharan Africa is presumably high but remains unknown. We did a systematic review to assess outcomes of acute kidney injury in sub-Saharan Africa and identify barriers to care.

Methods We searched PubMed, African Journals Online, WHO Global Health Library, and Web of Science for articles published between Jan 1, 1990, and Nov 30, 2014. We scored studies, and all were of medium-to-low quality. We made a pragmatic decision to include all studies to best reflect reality, and did a descriptive analysis of extracted data. This study is registered with PROSPERO, number CRD42015015690.

Findings We identified 3881 records, of which 41 met inclusion criteria, including 1403 adult patients and 1937 paediatric patients. Acute kidney injury in sub-Saharan Africa is severe, with 1042 (66%) of 1572 children and 178 (70%) 253 of adults needing dialysis in studies reporting dialysis need. Only 666 (64%) of 1042 children (across 11 studies) and 58 (33%) of 178 adults (across four studies) received dialysis when needed. Overall mortality was 34% in children and 32% in adults, but rose to 73% in children and 86% in adults when dialysis was needed but not received. Major barriers to access to care were out-of-pocket costs, erratic hospital resources, late presentation, and female sex.

Interpretation Patients in these studies are those with resources to access care. In view of overall study quality, data interpretation should be cautious, but high mortality and poor access to dialysis are concerning. The global scarcity of resources among patients and health centres highlights the need for a health-system-wide approach to prevention and management of acute kidney injury in sub-Saharan Africa.

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See **Comment** page e216

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Introduction

Acute kidney injury is associated with substantial morbidity and mortality worldwide, but data have been conspicuously missing from the Global Burden of Disease study.[1] Acute kidney injury refers to any sudden decline in kidney function, which can be reversible if detected early enough. Acute kidney injury can be community-acquired, resulting from an injury or infection before admission to hospital, or can be hospital-acquired, arising as a complication of hospital admission. Community-acquired acute kidney injury tends to occur in low-income countries, and in young people with few comorbidities, whereas hospital-acquired acute kidney injury tends to occur in high-income settings, and in older people (45–80 years), often with several comorbidities.[2] The burden of acute kidney injury in sub-Saharan Africa is unknown, but mortality is presumably high because of poor access to health care.

In a world meta-analysis,[3] the pooled incidence of acute kidney injury was 21·0% in adults and 33·7% in children, and mortality was 23·3% in adults and 13·8% in children. Only one of 154 included studies was from sub-Saharan Africa.[3] Most studies included patients with hospital-acquired acute kidney injury, contrasting with most acute kidney injury in sub-Saharan Africa, which is community-acquired.[3] Mortality was lower in countries with higher expenditure on health care, reflecting improved access to health care and dialysis in these countries.[3] In an update of this analysis, incidence and outcomes from 62 African studies were summarised in a table, but again excluded from the broader analysis.[2] The generalisability of these global findings to sub-Saharan Africa is therefore unknown.

Despite the absence of data for disease burden, the drive towards providing universal dialysis for acute kidney injury, which can be life-saving, is growing. In much of sub-Saharan Africa, dialysis is paid for out of pocket, at an estimated US$300 per episode of acute kidney injury for a child, and probably more for an adult.[4] In our experience, many patients cannot meet such costs and are forced to decline treatment. If provision of dialysis is to be sustainable in sub-Saharan Africa, data are needed to inform health policy decisions. In view of the present absence of epidemiological data, we have undertaken a systematic review to assess reported outcomes in patients with acute kidney injury in sub-Saharan Africa to highlight the real-world context of

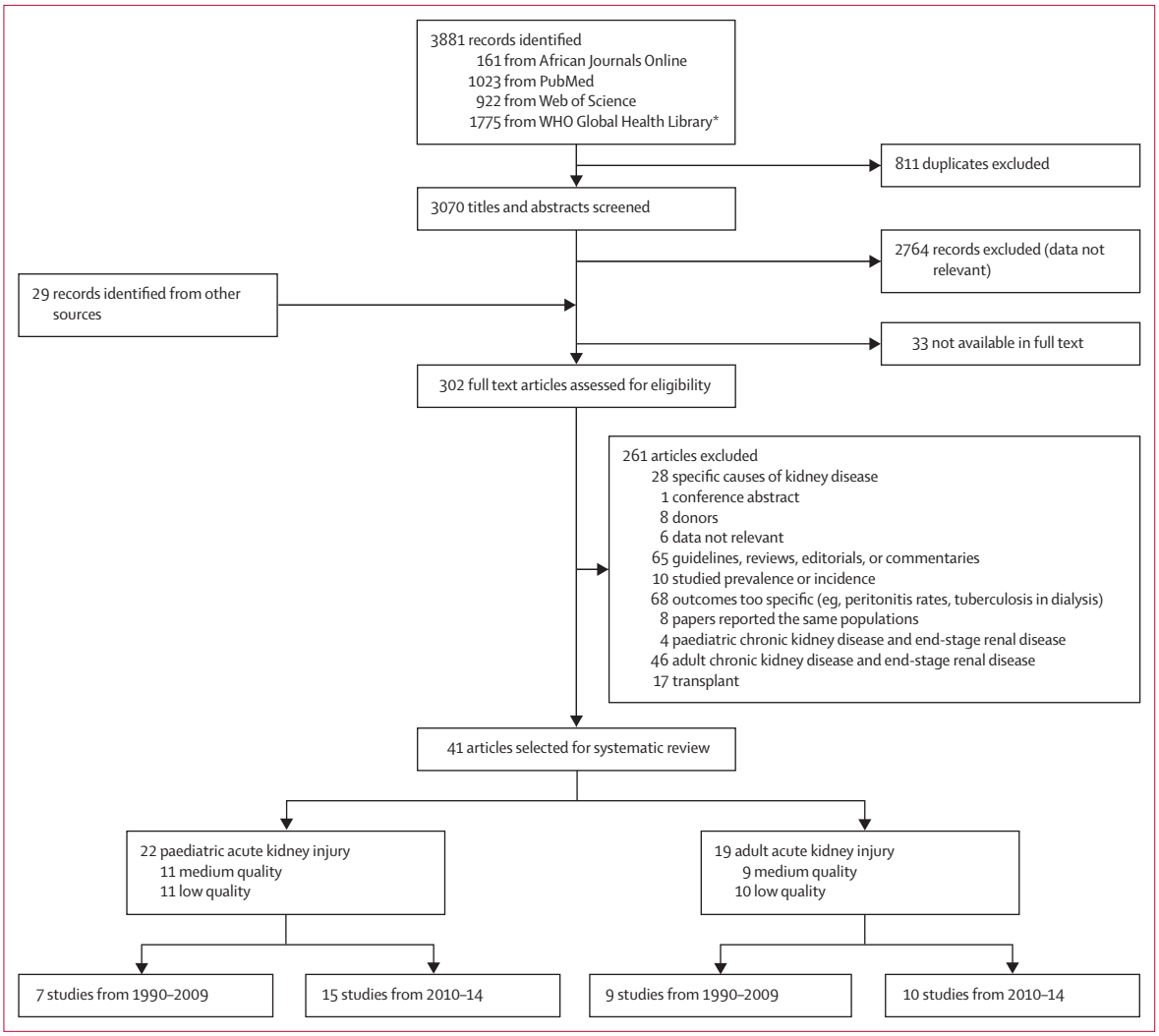

Figure 1: **Study selection**
*WHO Global Health Library includes African Index Medicus.

acute kidney injury in the region and to identify barriers to care that should be tackled to comprehensively address this important problem. This systematic review is highly relevant to understanding the challenges faced in management of acute kidney injury in sub-Saharan Africa, which are a crucial component of the disease burden.

Methods

Search strategy and selection criteria

See Online for appendix

We did a systematic review using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (appendix).[5] We searched PubMed, African Journals Online, the WHO Global Health Library, and Web of Science with relevant medical subject headings (appendix). We selected additional references through bibliographies from identified articles. We restricted the search to articles in English or French, published between Jan 1, 1990, and Nov 30, 2014. Outcomes of interest included access to dialysis, mortality, and recovery of renal function in cohorts of all patients admitted to hospital with acute kidney injury, irrespective of cause. We included variable definitions of acute kidney injury (clinical [oliguria, hyperkalaemia, or metabolic acidosis]; laboratory [urea or creatinine]; standardised diagnostic criteria; and need for dialysis). We excluded articles focusing exclusively on cohorts with single causes of acute kidney injury (eg, malaria), since outcomes would not be generalisable to the broader acute kidney injury population.[2] We excluded case reports. FAA and VAL screened titles and abstracts for eligibility. Articles meeting inclusion criteria and obtainable as full texts were reviewed in detail. This study is registered with PROSPERO, number CRD42015015690.

	Adult studies			Paediatric studies		
	1990–2009	2010–14	p	1990–2009	2010–14	p
Total number of studies	9	10	..	7	15	..
Countries	6	5	..	3	6	..
Patient inclusion period	1972–2007	1996–2013	..	1985–2004	2000–13	..
Total patients with acute kidney injury studied (pooled)	639	764	..	720	1217	..
Study duration (years)	5·2 (6·3)	4·9 (5·8)	..	11·3 (6·3)	4·8 (3·0)	..
Male patients (pooled)	339/601 (56%; n=8)	329/627 (52%; n=6)	0·17	459/713 (64%; n=6)	514/927 (55%; n=9)	<0·0001
Male/female ratio (means of individual studies)	1·5 (0·8)	1·2 (0·3)	0·31	1·9 (0·6)	1·3 (0·6)	0·14
Definitions of acute kidney injury used (number of studies)	9	9	0·14	6	11	0·023
Clinical	1	0	..	1	1	..
Laboratory (urea or creatinine)	5	2	..	1	0	..
Laboratory and clinical	0	0	..	4	1	..
(p)RIFLE, AKIN, or ADQI	0	3	..	0	4	..
Dialysis need	3	4	..	0	5	..
Clinical presentations (means of individual studies)						
Oliguria*	59·83% (SD 23·82, n=3)	67·25% (SD 18·58, n=4)	0·66	68·73% (SD 29·00, n=3)	73·02% (SD 8·1, n=6)	0·73
Hyperkalaemia†	30·4% (n=1)	25·10% (SD 23·6, n=3)	..	13·95% (SD 12·80, n=2)	28·60% (SD 15·60, n=4)	..
Metabolic acidosis‡	No data	53·87% (SD 20·44, n=3)	..	20·10% (SD 16·97, n=2)	42·20% (SD 26·51, n=3)	..

Data are number of studies, mean (SD), or percentage of patients (number of studies with outcome). p values reported for time periods 1990–2009 versus 2010–14. (p)RIFLE=(paediatric) risk, injury, failure, loss of function, and end-stage renal disease. AKIN=Acute Kidney Injury Network. ADQI=Acute Dialysis Quality Initiative. *Oliguria defined as urine output <400 mL per 24 h in adults, <300 mL per 24 h or <1 mL/kg/h in children, anuria, or not defined. †Definitions of hyperkalaemia variable, ≥5·5 mmol/L, ≥6·5 mmol/L, or not defined. ‡Definitions of metabolic acidosis variable, ≤10 mmol/L, ≤15 mmol/L, or not defined.

***Table 1*: Acute kidney injury study populations**

Quality assessment and data extraction

The quality of each study was assessed independently by two authors (VAL plus one of: WAO, AN, CO, GA, or FAA) using a checklist modified from Stanifer and colleagues[6] (appendix). Most studies were observational case series. Because no study met high-quality criteria (predominantly because no study represented all patients with acute kidney injury, and many did not describe inclusion or exclusion rates or missing data), rather than excluding almost all identified articles, we decided not to exclude any articles, to minimise bias and reflect reality as much as possible. Half of studies met medium-quality criteria (appendix). Data from individual studies were extracted into a Microsoft Excel database for analysis.

Data analysis

Because data were not uniform, we reported results with a descriptive approach and narrative synthesis.[7,8] We stratified data into adult and paediatric groups and analysed them separately. Where possible, we reported pooled estimates of outcome frequencies combining all studies, in parallel with means of reported individual study frequencies to show variability of reported outcomes.[8] We analysed differences in means with *t* tests and comparisons of proportions using the χ^2 test. More than half of the studies were published since 2010; therefore, to assess outcomes and detect changes over time, we further stratified data by publication before or after 2010.

We did descriptive statistics using Microsoft Excel and Statistics to Use.[9]

Role of the funding source

There was no funding source for this study.

Results

We identified 3070 studies through the literature search once duplicates were excluded. After screening titles and abstracts, we assessed 302 studies for eligibility (figure 1). 42 studies[10–50] from 13 countries satisfied inclusion criteria, reporting outcomes in all children and adults admitted to hospital with acute kidney injury. Two studies reported on the same patient cohort, therefore only the study with the most outcomes was included. Eight studies were prospective, 32 were retrospective, and one was cross-sectional. Studies are outlined in detail in the appendix. 13 adult and six paediatric studies included only patients

	Children (n=1643)*	Adults (n=993)†
Infection	380 (23%)	274 (28%)
Septicaemia	370	232
HIV	6	0
Tetanus	4	1
Pyelonephritis	0	12
Typhoid	0	7
Cholera	0	22
Glomerular disease	350 (21%)	76 (8%)
Acute glomerulonephritis	183	57
Nephrotic syndrome	115	10
Rapidly progressive acute glomerulonephritis	46	4
Lupus nephritis	5	5
Membranoproliferative acute glomerulonephritis	1	0
Nephrotoxin	270 (16%)	182 (18%)
Haemoglobinuria from:		
Plasmodium falciparum malaria haemolysis	198	34
G6PD deficiency haemolysis	18	0
Infection	0	41
Transfusion reaction	0	2
Autoimmune haemolytic anaemia	2	0
Herbal remedies ingestion	6	8
Holy water	0	7
Henna (para-phenylenediamine)	0	12
Unspecified drugs	0	17
Furosemide	5	0
ACE inhibitors	5	0
Cytotoxic drugs	5	0
Unspecified	31	61
Intravascular volume depletion or hypoperfusion	174 (11%)	50 (5%)
Gastroenteritis	169	42
Inadequate volume replacement before and after surgery	4	0
Severe haemorrhage	1	0
Unspecified	0	8
Obstructive uropathy	146 (9%)	46 (5%)
Renal stone	60	16
(Continued from previous column)		
Congenital anomaly of the kidney and the urinary tract		
Posterior urethral valves	32	0
Renal agenesis	4	0
Prune belly syndrome	1	0
Prostate	0	9
Malignancy	0	2
Schistosoma	0	2
Unspecified	49	17
Vascular disease or haemolysis	116 (7%)	11 (1%)
Haemolytic uraemic syndrome	111	1
Thrombotic thrombocytopenic purpura	2	0
Purpura fulminans	1	0
Renal vein thrombosis	1	1
Sickle cell crisis	1	0
Haemolysis, other	0	9
Medical, other	0	36 (4%)
Liver disease	0	15
Cardiac	0	8
Malignant hypertension	0	13
Malignancy	40 (2%)	19 (2%)
Birth asphyxia	27 (2%)	0
Obstetric or gynaecological	0	157 (16%)
Septic abortion	0	66
Pre-eclampsia or eclampsia	0	43
Pre-partum or post-partum haemorrhage	0	30
Ureter ligation after hysterectomy	0	7
Unspecified	0	11
Surgical	0	54 (5%)
Trauma, burns, or fractures	0	43
Postoperative	0	1
Other	0	10
Unspecified	140 (9%)	88 (9%)

G6PD=glucose-6-phosphate dehydrogenase. ACE=angiotensin converting enzyme. *17 paediatric studies. †14 adult studies.

***Table 2*: Causes of acute kidney injury in children and adults**

with acute kidney injury who received or needed dialysis; two adult studies included intensive care unit populations; and two adult studies included a small proportion of paediatric patients. Pooled studies included patients enrolled between April, 1972, and December, 2013.

Study populations are outlined in table 1. Pooled patients with acute kidney injury included 1403 adults and 1937 children. Six adult and nine paediatric studies described patients presenting with predominantly community-acquired acute kidney injury, and two paediatric studies reported the proportions of community-acquired acute kidney injury to be 72·8% and 82·9%.[14,16] In the remaining studies, most cases were probably community-acquired. Children ranged from birth to age 17 years, and mean age in adult studies ranged from 28·7 years to 44·4 years (appendix). The pooled proportion of male patients was significantly larger than that of female patients (57% men; p=0·005). Male predominance did not change in adults, but declined significantly in children over time (table 1). Reported frequencies of hyperkalaemia, metabolic acidosis, and oliguria are outlined in table 1. Acute kidney injury was attributed to intrinsic renal disease in 200 (pooled 56%) of 359 adults (across four studies) and 200 (pooled 41%) of 491 children (across six studies; data not shown). Detailed causes of acute kidney injury are shown in table 2. In adults

	Adult studies			Paediatric studies		
	1990–2009	2010–14	p	1990–2009	2010–14	p
Dialysis distribution	..	..	<0·0001	..	..	0·57
Haemodialysis	411 (82%; n=8)	558 (97%; n=8)	..	5 (4%; n=2)	114 (20%; n=5)	..
Peritoneal dialysis	86 (17%; n=2)	17 (3%; n=1)	..	122 (96%; n=6)	446 (77%; n=8)	..
Both	1 (<1%)	0	..	0	22 (4%; n=1)	..
CRRT	2 (<1%)	0	..	..	..	..
Studies with dialysis received as an inclusion criterion*	5	8	..	0	6	..
Indication for dialysis in acute kidney injury (pooled)	94/132 (71%; n=3)	84/121 (69%; n=1)	0·76	372/608 (61%; n=5)	670/964 (70%; n=6)	0·001
Access to dialysis (pooled)	44/94 (47%)	14/84 (17%)	..	119/372 (32%)	547/670 (82%)†	<0·0001
Access to dialysis (means of individual studies)	59·8% (SD 44·2)	16·7%	..	34·2% (SD 37·2)	54·0% (SD 28·9)	0·35

Data are number of patients (%) or number of studies. p values for 1990–2009 versus 2010–14. CRRT=continuous renal replacement therapy. *Studies with dialysis required or received as an inclusion criterion provided no information on non-dialysed patients or patients with acute kidney injury who did not need dialysis and therefore were excluded from this analysis. †When two studies from South Africa and Sudan are excluded, the dialysis access rate decreases to 31% and does not differ between 1990–2009 and 2010–14.

***Table 3*: Indication for dialysis and access to dialysis in children and adults with acute kidney injury**

and children, infection, including malaria, accounted for more than 30% of acute kidney injury.

Delays of up to 3 weeks between onset of symptoms and presentation to hospital were described in three adult studies.[31,36,38] One paediatric study reported a mean delay of 6 days between symptom onset and presentation, and two studies described delay in presentation among 50–80% of children (appendix).[11,15,29]

Definitions used for diagnosis of acute kidney injury have changed over time (table 1). Standardised diagnostic criteria for acute kidney injury (risk, injury, failure, loss of function, and end-stage renal disease [RIFLE] and paediatric RIFLE [pRIFLE]; Acute Kidney Injury Network [AKIN]; and Acute Dialysis Quality Initiative) were used in 35% of studies that reported definitions used published after 2010 compared with none before 2010.

1075 adults and 609 children received dialysis (table 3). Haemodialysis predominated among adults (969 [90%] of 1075) and peritoneal dialysis predominated among children (568 [80%] of 709). 19 of the 41 studies included only patients who needed or received dialysis and therefore could not be used to calculate dialysis indication or access rates.

Access to dialysis was defined as the proportion of patients with acute kidney injury who received dialysis when indicated (table 3). In four studies, 178 of 253 adults needed dialysis, giving a pooled dialysis indication rate of 70%. Among these 178 adults, the pooled dialysis access rate was 33%. The mean dialysis access rate across adult studies was 49·1% (SD 42·3). 11 studies reported dialysis need in 1042 of 1572 children with acute kidney injury, giving a pooled dialysis indication rate of 66% (table 3). In these 1042 children, the dialysis access rate was 64%. The mean dialysis access rate across studies was 45·0% (SD 32·8; range 9·7–100). In pooled analyses, dialysis indication rate and dialysis access rate in children increased significantly over time (table 3; p<0·0001). However, when data from South Africa and Sudan (countries with government-sponsored dialysis and paediatric acute kidney injury access rates of 100% and 95%, respectively) were excluded from this analysis, the pooled dialysis access rate after 2010 decreased to 31% (156 of 509 children received dialysis), which does not differ significantly from the rate before 2010.

One study described a delay of 3·3 days (SD 1·9; range 1–9) between admission to hospital and initiation of dialysis owing to the search for resources to pay for dialysis, others reported patient deaths while the search for resources was underway, or patients leaving hospital against medical advice because of inability to afford dialysis (appendix).[13,25,45]

Mortality was reported in 17 adult studies and 21 paediatric studies (table 4). Of 1077 adults, 346 died, giving a pooled mortality of 32%. Of 1842 children, 627 died, giving a pooled mortality of 34%. Pooled mortality decreased significantly in both adults and children over time, although the ranges of individual study mortalities were highly variable (p<0·0001). Mortality associated with specific causes of acute kidney injury is shown in the appendix.

When stratified by whether dialysis, when indicated, was received or not, pooled mortality was significantly higher in adults (86% *vs* 30%; p<0·0001) and children (74% *vs* 30%; p<0·0001) who did not receive at least one dialysis session. Nine studies reported consistent findings in adults and children from the same cohort, suggesting this may not merely be a centre effect (appendix). Mortality in children was not different between those who received haemodialysis and those who received peritoneal dialysis. Overall mortality reported in children with acute kidney injury who did not need dialysis was lower than in those who received dialysis (16·22% *vs* 28·54%; p=0·13).

Major predictors of poor outcomes in several studies were late presentation and inability to pay for dialysis.[18,36] Numbers of patients lost to follow-up or leaving against medical advice were high in some studies (table 4), showing the challenges of patient care and clinical research in sub-Saharan Africa.

Renal recovery, defined as independence from dialysis, improvement in serum creatinine after acute kidney injury,

	Adult studies			Paediatric studies		
	1990–2009	2010–14	p	1990–2009	2010–14	p
Overall mortality						
Mortality (pooled)	237/639 (37%; n=9)	109/438 (25%; n=8)	<0·0001	285/720 (40%; n=7)	342/1122 (30%; n=14)	<0·0001
Mortality (means of individual studies)	38·7% (20·6)	29·2% (24·5)	0·40	40·5% (8·3)	30·4% (14·4)	0·11
Mortality without dialysis when needed						
Mortality without dialysis when needed (pooled)	43/50 (86%; n=2)	NA	..	179/247 (72%; n=4)	45/57 (79%; n=3)	0·32
Mean mortality without dialysis (means of individual studies)	82·4% (12.8)	NA	..	72·9% (18·8)	90·0% (17·3)	0·27
Mortality with dialysis						
Mortality with dialysis (pooled)	161/500 (32%; n=8)	78/288 (27%; n=6)	0·13	28/119 (24%; n=5)	184/585 (31%; n=10)	0·09
Mean mortality with dialysis (means of individual studies)	28·0% (15·7)	35·1% (26·1)	0·54	16·4% (11·5)	34·6% (20·1)	0·09
Mean mortality haemodialysis (means of individual studies)	27·3% (14·13; n=7)	33·46 % (27·00; n=6)	0·61	57·0% (39·9; n=3)		0·27*
Mean mortality peritoneal dialysis (means of individual studies)	25% (n=1)	NA	NA	33·6% (27·4; n=9)		..
Mortality when dialysis not indicated						
Mortality when dialysis not indicated (pooled)	23/43 (53%†; n=2)	NA	..	36/232 (16%; n=4)	43/285 (15%; n=4)	0·84
Mortality, acute kidney injury not needing dialysis (means of individual studies)	30·3% (42·8)	NA	..	22·2% (17·1)	10·2% (8·4)	0·25
Other outcomes						
Recovery of renal function in survivors (pooled)	58/78 (74%; n=2)	72/159 (45%; n=4)	<0·0001	152/172 (88%; n=3)	515/714 (72%; n=8)	<0·0001
Residual chronic kidney disease in survivors (pooled)‡	6/73 (8%; n=1)	18/113 (16%; n=2)	0·1	23/143 (16%; n=2)	45/533 (8%; n=3)	0·007
Left hospital against medical advice (pooled)	0	6/62 (10%; n=1)	..	10/183 (5%; n=2)	33/814 (4%; n=5)	0·4
Lost to follow-up (pooled)	28/264 (11%; n=2)	6/17 (35%; n=1)	..	116/334 (35%; n=2)	20/700 (3%; n=2)	<0·0001

Data are mean % (SD) or mean (%; number of studies with outcome). p values for 1990–2009 versus 2010–14. *Comparison between haemodialysis and peritoneal dialysis in children. †One study included high-comorbidity patients in intensive care units. ‡Chronic kidney disease not specifically defined, generally non-requirement for dialysis but non-return of renal function to normal parameters by discharge or loss to follow-up.

Table 4: **Outcomes in children and adults with acute kidney injury**

or both, was reported in 17 studies (table 4). The pooled rate of renal recovery was 130 (55%) of 237 (six studies) in adult survivors and 667 (75%) of 886 (11 studies) in child survivors. The pooled rate of residual chronic kidney disease, defined as persistence of renal dysfunction but not needing dialysis at time of discharge, was 24 (13%) of 186 adults (three studies) and 68 (10%) of 676 children (five studies). These outcomes were not routinely reported or systematically defined, and some studies had substantial loss to follow-up, so the true rates remain unknown.

Discussion

The aim of this systematic review was to describe the real-world context of patients diagnosed with acute kidney injury in sub-Saharan Africa. We identified 41 studies published during 25 years reporting access to dialysis when needed, mortality, and renal outcomes in cohorts of all patients with acute kidney injury.

Most patients presented with severe acute kidney injury, with 70% of adults and 66% of children needing dialysis (stage 3 acute kidney injury). This dialysis need contrasts strongly with the pooled world need for dialysis in patients with acute kidney injury of 11%, because 80% of all patients worldwide had stage 1 (mild) acute kidney injury.[4] These opposing observations suggest that acute kidney injury is a more aggressive disorder in sub-Saharan Africa than elsewhere; however, this is more likely to be a result of late presentation to hospital and reliance on clinical criteria for diagnosis, which might only become apparent at an advanced stage. Many studies commented on delay in patient presentation, not uncommonly with oliguria and advanced uraemia at diagnosis.

When dialysis was needed, the pooled dialysis access rate was 33% in adults and 64% in children, although rates were as low as 10% in some studies. Results of a survey of availability of paediatric services in Nigeria showed that more than 50% of facilities did not have dialysis capability.[51] When patients did gain access to dialysis, most adults received haemodialysis, showing the absence of peritoneal dialysis in many centres.[32,34,36] In

children, peritoneal dialysis predominated, owing to body size limitations and absence of haemodialysis facilities.[11,23,28] Paediatric peritoneal dialysis was sometimes done with modified alternative catheters and fluids when appropriate resources were unavailable.[23]

The overall pooled mortality was 32% in adults and 34% in children with acute kidney injury. These rates are much higher than the pooled world rates of 23·3% in adults and 13·8% in children, possibly showing the increased severity of documented acute kidney injury in sub-Saharan Africa and low access to dialysis.[3] The more than two times higher mortality in children in sub-Saharan Africa compared with worldwide mortality is especially concerning. How the overall data might be skewed by the high proportion of studies exclusively on dialysed patients is difficult to predict. Pooled mortality in those who received dialysis was 30% in adults and children, lower than the world mortality among dialysed patients with acute kidney injury of 46%.[2] The lower dialysis mortality in sub-Saharan Africa compared with elsewhere might reflect the relative absence of patient comorbidities and more frequent community-acquired acute kidney injury, despite frequent premature discontinuation of dialysis because of cost.[38]

However, a substantial proportion of patients with acute kidney injury in sub-Saharan Africa did not receive dialysis when needed and experienced very high mortality rates. These poor outcomes show the severity of patient illness and delayed presentation, delays imposed by searching for funds after admission to hospital, and the erratic infrastructure.[13,18,29,38,45] However, mortality among these undialysed patients was not inevitable, emphasising the value of conservative management and prompt treatment of underlying disease in the absence of dialysis.[24] Availability of the needed resources might also be inconsistent in sub-Saharan Africa. Resources reported during the included studies are listed in the appendix. A survey of 66 intensive care facilities in the Democratic Republic of the Congo reported that crystalloids were available in 100% of units, but that availability of antibiotics and other necessities was variable.[52] Serum creatinine was never available in 75·8% of units. Dialysis was not available in any units.

Most adults and children surviving acute kidney injury recovered renal function, although roughly 10% had residual renal dysfunction. This high rate of persistent renal dysfunction might be a result of the initial severity of acute kidney injury, or might highlight the challenges in excluding underlying chronic kidney disease without access to diagnostic tests. Very few cohorts had long-term follow-up, therefore these percentages could be an overestimate and some patients might have continued to improve over time.

Several barriers to access to care for acute kidney injury were identified through this study, as shown in figure 2. First, the low overall patient numbers reported suggest that many patients with acute kidney injury are not diagnosed or treated. Second, male patients predominate, probably showing some discrimination against women. Third, poor patient resources led to delays in admission to hospital and use of traditional medicine, which might be especially harmful in the setting of dehydration, for example, and worsen kidney injury. Fourth, delays occur in referral from peripheral health-care sites to sites where renal care is available. Finally, delays occur after admission to hospital because patients need to search for funds to pay for dialysis or because supplies, staffing, or resources of the hospital are erratic. Each of these delays might have a seemingly obvious cause, but if a holistic approach is to be taken to prevent acute kidney injury, much research, including clinical, epidemiological, and anthropological study, is needed to investigate all contributors to such barriers. The expectation that most patients can pay for dialysis, even when heavily subsidised, is probably unrealistic, since even meagre user-fees are a hindrance to access to basic health care in low-income settings.[53] The predominance of male

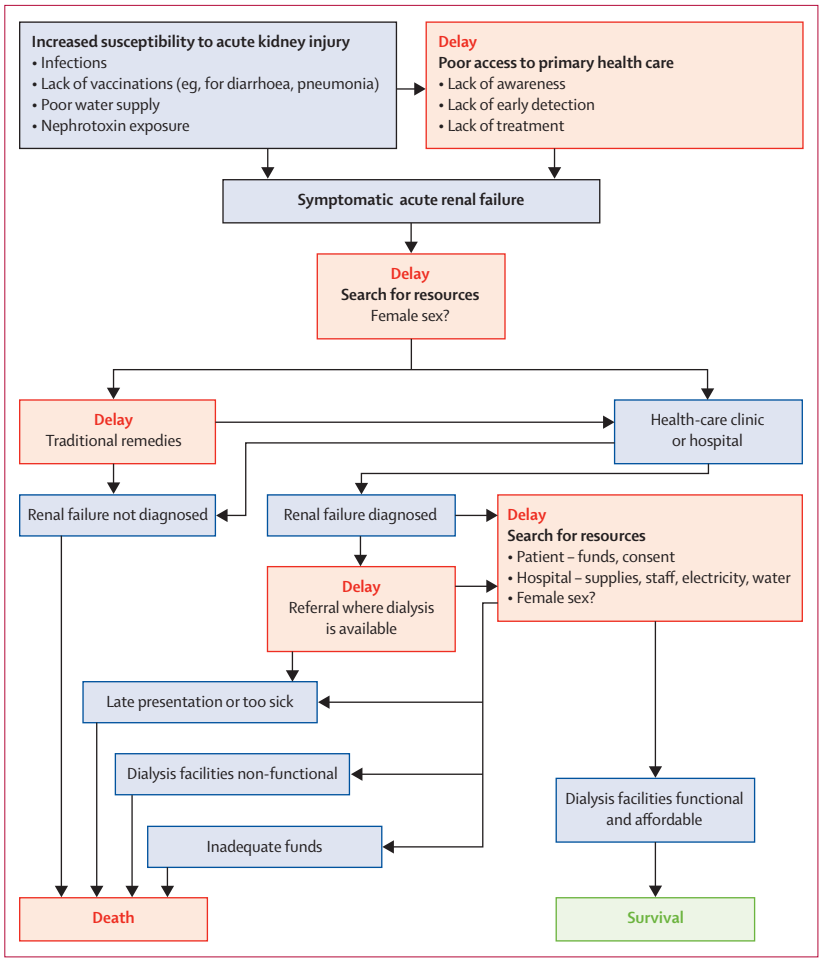

Figure 2: **Barriers to care in acute kidney injury**
Outcomes shown for each pathway (survival or death) are the most likely outcomes, but are not inevitable (table 4).

patients might reflect a true increased susceptibility to renal disease (eg, urogenital abnormalities in boys), but more probably reflects the relative absence of economic and decision-making power among women, and is consistent with findings in other low-resource regions.[54,55]

Although reported observations seem to be mostly consistent across studies, this systematic review has substantial limitations. In most countries in sub-Saharan Africa, access to diagnosis and specialist renal care for acute kidney injury is scarce, and is heavily reliant on out-of-pocket payments by patients. The patients reported in the reviewed studies are therefore those who had the resources to be diagnosed with acute kidney injury, some of whom were also able to access dialysis. These studies do not represent the many patients with acute kidney injury in sub-Saharan Africa for whom the needed health services are beyond reach.

The observational and historical nature of most studies, coupled with a high proportion of missing data, frequent patient loss to follow-up, variability in acute kidney injury definitions, and representation of data from only 13 countries all diminish the robustness of data interpretation. Such weaknesses have led to exclusion of these studies from existing meta-analyses, and acute kidney injury in sub-Saharan Africa has therefore remained a so-called black box in the world scientific literature on acute kidney injury. Our decision to include all obtainable studies was intentional to try to mitigate publication bias that would be exacerbated with further study selection, and to best capture the reality of daily challenges faced by patients and nephrologists in sub-Saharan Africa. Our inclusion of all comers also strengthens the generalisability of the findings to the general acute kidney injury population. However, descriptive analysis cannot account for different study weights or quality, and the conclusions are therefore less robust than in a meta-analysis. The severity of reported acute kidney injury might show a bias towards testing the most symptomatic patients, which could overestimate poorer outcomes, although patients who survived the delay in presentation to hospital might have a propensity to survival. Abstracts of nine acute kidney injury articles were not obtainable in full text, but the outcomes described suggest consistency with the main findings of this study and would therefore be unlikely to alter the conclusions.

Highlighting real-world outcomes and challenges, despite study limitations, is important to inform health-systems-wide planning and policy development for acute kidney injury in regions where resources are scarce and many health-care priorities are competing. The increasing number of publications over time highlights growing expertise, but also an urgency in the specialty. This study also highlights the important limitations of previous studies. Study quality scores and checklists should be considered prospectively in any ongoing or planned research on acute kidney injury in sub-Saharan Africa to optimise study design, data collection, and accuracy of reporting, so that future studies can further understanding of the true burden of acute kidney injury in sub-Saharan Africa and reliably inform policy making.

The published outcomes of acute kidney injury in patients in sub-Saharan Africa show the complexities of access to timely and appropriate renal care in the region. Several barriers to diagnosis and care of acute kidney injury are evident, the most consistent of which are delays in reaching hospital, cost of care, erratic functioning or supply of hospital resources, and female sex. If a programme for prevention and treatment of acute kidney injury is to be effective and sustainable, each barrier will need to be understood and overcome.

Contributors

WAO and AN scored the papers, analysed data, and wrote the manuscript. CO and GA scored the papers and wrote the manuscript. FAA did the literature search, scored papers, and wrote the manuscript. SN and JP interpreted data and wrote the manuscript. VAL did the literature search, scored papers, analysed data, and wrote the manuscript. All authors contributed to development of study concept and editing of the manuscript. All authors approved the final manuscript.

Declaration of interests

We declare no competing interests.

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PAPER 2

OUTCOMES IN ADULTS AND CHILDREN WITH END-STAGE KIDNEY DISEASE REQUIRING DIALYSIS IN SUB-SAHARAN AFRICA: A SYSTEMATIC REVIEW

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Outcomes in adults and children with end-stage kidney disease requiring dialysis in sub-Saharan Africa: a systematic review

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Summary

Background The burden of end-stage kidney disease (ESKD) in sub-Saharan Africa is unknown but is probably high. Access to dialysis for ESKD is limited by insufficient infrastructure and catastrophic out-of-pocket costs. Most patients remain undiagnosed, untreated, and die. We did a systematic literature review to assess outcomes of patients who reach dialysis and the quality of dialysis received.

Methods We searched PubMed, African Journals Online, WHO Global Health Library, and Web of Science for articles in English or French from sub-Saharan Africa reporting dialysis outcomes in patients with ESKD published between Jan 1, 1990, and Dec 22, 2015. No studies were excluded to best represent the current situation in sub-Saharan Africa. Outcomes of interest included access to dialysis, mortality, duration of dialysis, and markers of dialysis quality in patients with ESKD. Data were analysed descriptively and reported using narrative synthesis.

Findings Studies were all of medium to low quality. We identified 4339 studies, 68 of which met inclusion criteria, comprising 24 456 adults and 809 children. In the pooled analysis, 390 (96%) of 406 adults and 133 (95%) of 140 children who could not access dialysis died or were presumed to have died. Among those dialysed, 2747 (88%) of 3122 adults in incident ESKD cohorts, 496 (16%) of 3197 adults in prevalent ESKD cohorts, and 107 (36%) of 294 children with ESKD died or were presumed to have died. 2508 (84%) of 2990 adults in incident ESKD cohorts discontinued dialysis compared with 64 (5%) of 1364 adults in prevalent ESKD cohorts. 41 (1%) of 4483 adults in incident ESKD cohorts, 2280 (19%) of 12 125 adults in prevalent ESKD cohorts, and 71 (19%) of 381 children with ESKD received transplants. 16 studies reported on management of anaemia, 17 on dialysis frequency, eight on dialysis accuracy, and 22 on vascular access for dialysis

Interpretation Most patients with ESKD starting dialysis in sub-Saharan Africa discontinue treatment and die. Further work is needed to develop equitable and sustainable strategies to manage individuals with ESKD in sub-Saharan Africa.

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Introduction

Chronic kidney disease (CKD) is an increasing, but still underappreciated, contributor to the global burden of disease.[1] Best estimates from sub-Saharan Africa suggest 12–23% of adults have CKD and are therefore at risk of developing end-stage kidney disease (ESKD).[2–4] Since symptoms are largely non-specific and manifest late, diagnosis of CKD, especially at an early treatable stage, is easily missed.

Once the kidneys fail, renal replacement therapy by dialysis or transplantation is the only means of survival. Findings from studies in the past 5 years[5,6] have suggested that between 2·3 million and 3·2 million people die yearly as a result of no access to dialysis. Estimation of the anticipated incidence of ESKD based on the prevalence of hypertension and diabetes suggests that only 1·5% of those requiring renal replacement therapy in sub-Saharan Africa receive it.[5] Others reported a gap between those who require and receive dialysis of over 84% in sub-Saharan Africa.[6] There is no African renal registry, but reported dialysis incidence tends to be higher than prevalence in sub-Saharan Africa, suggesting high mortality among patients with ESKD.[5–8] Where available, haemodialysis predominates because of frequent unavailability and higher costs of peritoneal dialysis and little availability of transplantation.[9,10] In South Africa and Sudan, governments provide dialysis for ESKD. In South Africa, state-funded dialysis is accessed through a rationing process; in Sudan dialysis is offered to all, but at a reduced frequency (haemodialysis two instead of three times per week).[11,12] In other sub-Saharan African countries, most expenses are paid out of pocket.[12–15] Therefore, in most of sub-Saharan Africa, patients with prevalent ESKD represent the elite few with enough resources to access long-term renal replacement therapy.

Dialysis outcomes are associated with the quality of dialysis delivered, which depends on the amount (ie, dose), duration, and frequency of dialysis; management of complications including anaemia; blood pressure; phosphate control; and laboratory monitoring. In haemodialysis, type of vascular access also affects morbidity and mortality.

We did a systematic review to explore outcomes and quality of dialysis in patients with incident and prevalent

Research in context

Evidence before this study

Data on epidemiology and outcomes of end-stage kidney disease (ESKD) in sub-Saharan Africa are sparse. We did a systematic review of the literature to understand outcomes in patients with ESKD managed under existing circumstances in sub-Saharan Africa. We searched PubMed, African Journals Online, the WHO Global Health Library, and Web of Science between Jan 1, 1990, and Dec 22, 2015, with relevant medical subject headings. Additional references were found through screening of reference lists from identified articles. All retrieved and selected articles were published in English or French. No previous systematic reviews on this topic were identified.

Added value of this study

This study is, to our knowledge, the first to systematically analyse outcomes and quality of dialysis received in patients with ESKD in sub-Saharan Africa from several countries and centres. We found high mortality among patients with incident ESKD. Mortality was lower in patients with prevalent ESKD who had dialysis, which provides reason for optimism, but raises the important ethical question of how such dialysis could be sustainable on a broader scale in low-income countries with other health priorities and where opportunity costs (ie, the proportion of budget allocated to dialysis is not available for allocation to other health issues) are high. The quality of dialysis delivered is generally low, mostly because of economic factors.

Implications of all the available evidence

The increasing numbers of publications from sub-Saharan Africa in recent years is testament to the growing expertise in the region. As expertise grows, the health system must adapt; therefore, studies such as this are important initial steps to raise awareness of the clinical problem of ESKD as well as the large ongoing knowledge gaps among policy makers and the international community.

ESKD in sub-Saharan Africa. Understanding the local realities of management of ESKD is important to highlight the daily clinical and moral dilemmas faced by clinicians, patients, and families when dialysis is paid for out of pocket, and to inform pragmatic policy development about ESKD care in resource-limited settings.

Methods

Search strategy and selection criteria

We registered our systematic literature review with PROSPERO (CRD42015015690) and completed it according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[16] We searched PubMed, African Journals Online, the WHO Global Health Library, and Web of Science from Jan 1, 1990, to Dec 22, 2015, with relevant medical subject headings (appendix p 1). The search was restricted to publications in English and French. Additional references were identified through bibliography searches. Criteria for inclusion were all studies reporting outcomes related to access to dialysis, mortality, duration of dialysis, and markers of dialysis quality in patients with ESKD who needed or received dialysis in sub-Saharan Africa. Articles focusing exclusively on specific outcomes or subpopulations, such as infections, and those reporting transplantation outcomes were excluded, as were case reports (appendix p 1). Two authors (FA and VAL) screened titles and abstracts for eligibility. Articles meeting inclusion criteria and obtainable as full texts were reviewed in detail. Incident cohorts were defined as those reporting outcomes in patients with a new diagnosis of ESKD who needed, but either started or did not receive, dialysis. Prevalent ESKD cohorts were defined as those reporting outcomes in patients receiving long-term dialysis.

See Online for appendix

Quality assessment and data extraction

Study quality was assessed independently by two authors (VAL plus GA, CO, WAO, FA, or AN), as described previously (appendix pp 2–3).[3,17] All articles meeting inclusion criteria were included in an attempt to minimise further bias and to reflect the current situation in sub-Saharan Africa, as reported previously.[17] Individual study data were extracted into Microsoft Excel (Redmond, WA, USA; appendix p 4).

Data analysis

In view of the variability in definitions of ESKD, length of follow-up, proportions of loss to follow-up, study sizes, and outcomes reported per study, data were analysed descriptively and reported using narrative synthesis.[18,19] Where possible, outcomes were reported within time-frames for perspective; however, these data were not routinely available. Study populations were stratified by participant age (adult or paediatric) and by incident or prevalent cohorts. Outcomes were analysed separately for adults with incident and prevalent ESKD to test the hypothesis that outcomes are improved among patients with ESKD in sub-Saharan Africa who can achieve long-term dialysis. Similarly, in view of more scarce resources and probably a lower ability to pay for ESKD care for children than adults in sub-Saharan Africa, outcomes in adult and paediatric populations were analysed separately. Data were reported as pooled estimates of outcome frequencies; however, in view of the variability between studies, the same outcomes are also reported in parallel as means (with SDs) of frequencies reported in individual studies, to show the breadth of interstudy variability of the various outcomes. Study denominators vary depending on the outcomes reported. Adults with incident and those with prevalent ESKD are reported separately; children were analysed overall because of the

small number of studies. Statistical analyses were not done because of the intrinsic differences between adults with incident versus prevalent ESKD and between adults and children, rendering comparisons artificial.

Role of the funding source

There was no funding source for this study. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

4339 records were found, of which 1151 were excluded; 386 of 3188 screened studies underwent full review (figure 1), including one registry report from South Africa. No study was of high quality, mainly because participants were not representative of the larger ESKD population and because of missing data. 68 studies (56 adult, 12 paediatric) from 15 countries satisfied inclusion criteria, 49 of which were published from 2010 onwards. 34 of the 68 studies met medium-quality criteria. 26 adult and ten paediatric studies included patients with incident ESKD, 30 adult and two paediatric studies included patients with prevalent ESKD (appendix pp 5–11), and 37 adult and two paediatric studies included only patients who received dialysis. Ten studies provided details of missing data. 16 adult studies were prospective, seven cross-sectional, and 33 retrospective. Two paediatric studies were prospective and ten retrospective. Study duration ranged from 0·08 years to 19 years. All 12 paediatric and 26 of the adult studies were from academic hospitals; 24 adult studies were from city hospitals or haemodialysis units; three were from private dialysis units; and three reported whole-country data. 24 456 adults (10 354 with incident and 14 102 with prevalent ESKD) and 809 children (736 incident and 73 prevalent) were included in analyses (table 1).[12,13]

Mean patient ages ranged from 35·6 years (SD 13·2) to 58·2 years (SD 15·0) in adult studies and from 9·8 years (range 3 months to 17 years) to 11·5 years (SD 3·0) in paediatric studies. Males predominated among adults and children (table 1). The term CKD was often used synonymously with ESKD. The definitions of CKD and ESKD used are reported in table 1. The causes of CKD

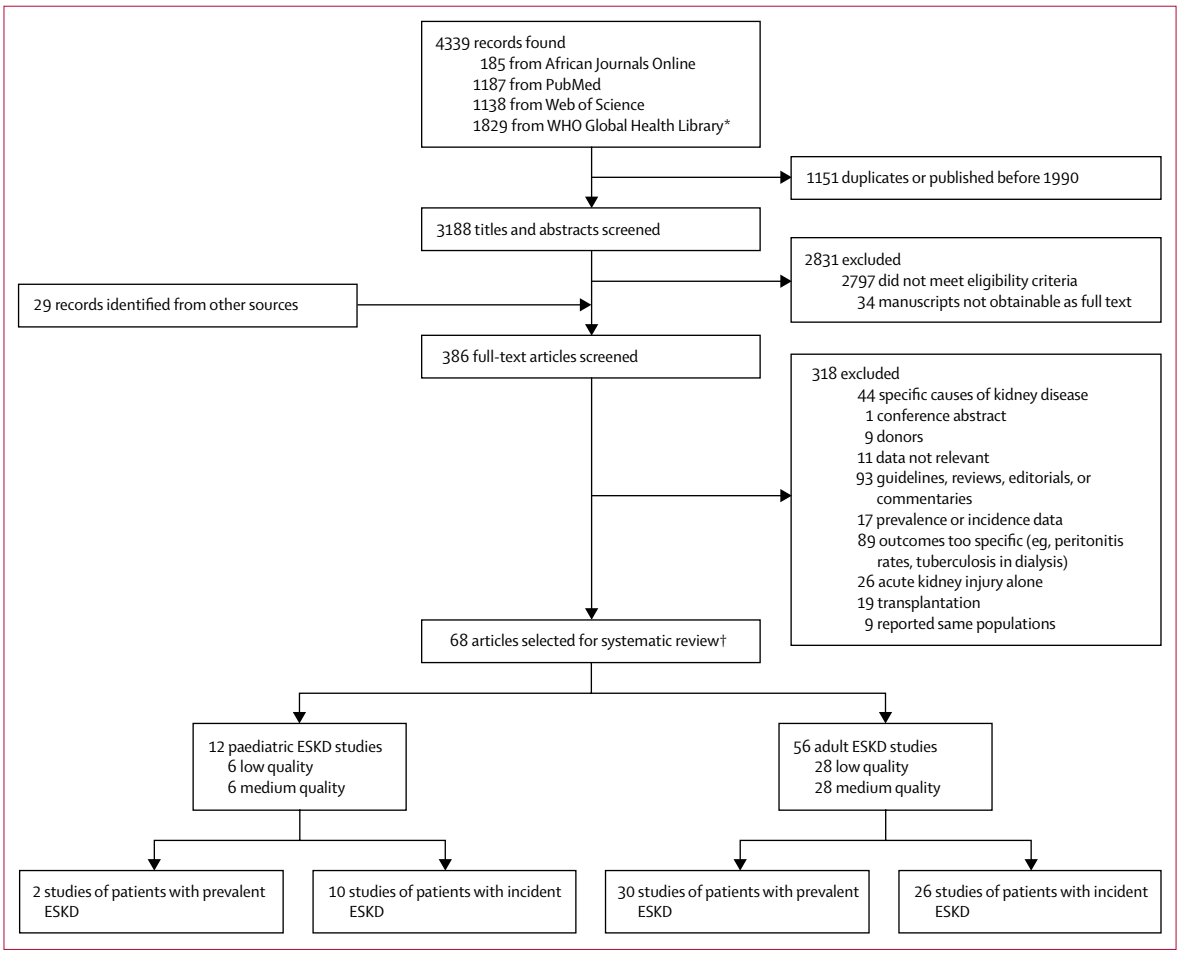

Figure 1: **Study selection**
ESKD=end-stage kidney disease. *Includes African Index Medicus. †39 had receipt of dialysis as an inclusion criterion.

	Adult studies			Paediatric studies (n=12)
	Overall (n=56)	Incident ESKD (n=26)	Prevalent ESKD (n=30)	
Number of countries	14	8	12	4
Patient inclusion period	1976–2014	1976–2013	1987–2014	1995–2013
Total number of patients with CKD or ESKD	24 456	10 354	14 102	809
In South Africa and Sudan only	15 063	2586	12 477	398
Excluding South Africa and Sudan	9393	7768	1625	411
Study duration (years)*	4·0 (4·5)	5·8 (5·1)	2·1 (2·3)	6·1 (2·8)
Sex†				
Male	13 655/22 152 (62%)	5682/9401 (60%)	7973/12 751 (63%)	439/748 (59%)
Female	8497/22 152 (38%)	3719/9401 (40%)	4778/12 751 (37%)	309/748 (41%)
Male:female ratio, individual studies†	1·98 (1·09)	1·72 (0·78)	2·20 (1·39)	1·46 (0·34)
Definitions of CKD or ESKD used				
Clinical	7	7	0	2
Laboratory (creatinine thresholds)	9	9	0	6
ESKD, glomerular filtration rate <15 mL/min	7	7	0	0
KDIGO or KDOQI	4	4	0	3
Dialysis requirement	41	11	30	2
Not mentioned	1	1	0	3

Data are mean (SD) or n/N (%), unless otherwise specified. CKD=chronic kidney disease. ESKD=end-stage kidney disease. KDIGO=Kidney Disease Improving Global Outcomes. KDOQI=Kidney Disease Outcomes Quality Initiative. *Data missing for four studies in adults with prevalent ESKD and one paediatric study. †Data missing for ten studies in adults (five incident ESKD and five prevalent ESKD) and four in children.

Table 1: **Study populations**

and ESKD were reported in 40 adult and 12 paediatric studies (appendix p 12).

The proportion of patients with incident ESKD who were able to access dialysis is outlined in table 2. Pooled analysis showed that 4221 of 8253 adults (51%; 15 studies) and 211 of 347 children (61%; eight studies) received at least one dialysis session. The mean percent access to dialysis across individual studies was 39·1% (SD 25·7) in adults and 47·4% (30·6) in children. Of 3692 adults with incident ESKD, 2980 (81%) received haemodialysis and 712 (19%) received peritoneal dialysis (16 studies); these numbers were 11 186 (84%) and and 2194 (16%) among 13 380 adults with prevalent ESKD (26 studies), and 128 (46%) and 149 (54%) among 277 children (ten studies).

Dialysis duration was reported in 35 adult and eight paediatric studies (table 2). Among those who started dialysis, 2572 of 4354 adults (59%; 23 studies) and 94 of 192 children (49%; six studies) discontinued dialysis. In adults, 2508 of 2990 (84%; 13 studies) incident and 64 of 1364 (5%; ten studies) prevalent patients discontinued dialysis after a mean of 6·5 (SD 5·3) sessions. The pooled proportion of children discontinuing dialysis was 94 of 192 (49%; six studies), and the mean percentage was 76·2% (SD 33·6). The proportions of adults and children continuing dialysis for at least 3 months and at least 12 months are shown in table 2. The pooled proportion of adults with prevalent ESKD remaining on dialysis for at least 3 months was 3029 of 3575 (85%; ten studies) and the mean of individual study frequencies was 63·4% (SD 24·0), compared with a pooled proportion of 295 of 3104 (10%; 16 studies) and mean of individual study frequencies of 14·1% (SD 12·6) in adults with incident ESKD. The durations of dialysis received in individual studies are shown in the appendix (pp 5–11). Compared with the full cohort, when studies from South Africa and Sudan were excluded, the proportions of people who discontinued dialysis were higher among both adults and children (78% and 86%, respectively; appendix p 13).

In the pooled analyses, overall known study mortality was higher in adults (3446 [32%] of 10 874; 35 studies) than in children (159 [24%] of 656; ten studies) and in incident (2966 [39%] of 7677; 17 studies) than in prevalent (480 [15%] of 3197; 18 studies) adult cohorts. However, overall study mortality might not represent ESKD mortality, because some studies included patients with CKD who did not require dialysis, and most did not account for patients lost to follow-up or leaving hospital against medical advice. 27 of 143 children (19%; three studies) had left hospital against medical advice, whereas 557 of 3087 adults (18%; 12 studies) and 188 of 675 children (28%; eight studies) were lost to follow-up (table 3). We presumed that these patients probably died without further treatment. Including these patients and those who discontinued dialysis in the pooled analysis, known and presumed mortality occurred in 5128 of 9057 adults (57%; 39 studies) and 266 of 426 children (62% 11 studies). Mortality was higher among adults with incident (4632 [79%] of 5860; 21 studies) than among those with prevalent ESKD (496 [16%] of 3197; 18 studies).

	Adult studies			Paediatric studies
	Overall	Incident	Prevalent	
Access to dialysis				
Pooled	4221/8253 (51%; 15)	4221/8253 (51%; 15)	NA	211/347 (61%; 8)
Individual studies	39·1% (25·7; 16)	39·1% (25·7; 16)	NA	47·4% (30·6; 8)
Not dialysed although indicated				
Pooled	3277/6797 (48%; 11)	3277/6797 (48%; 11)	NA	106/323 (33%; 7)
Individual studies	56·6% (19·5; 11)	56·6% (19·5; 11)	NA	41·6% (21·4; 7)
Known to stop dialysis although needed				
Pooled	2572/4354 (59%; 23)	2508/2990 (84%; 13)	64/1364 (5%; 10)	94/192 (49%; 6)
Individual studies	51·4% (41·4; 23)	79·7% (27·5; 13)	14·7% (23·0; 10)	76·2% (33·6; 6)
Continued dialysis ≥3 months*				
Pooled	3324/6589 (50%; 26)	295/3014 (10%; 16)	3029/3575 (85%; 10)	66/190 (35%; 7)
Individual studies	33·1% (32·9; 26)	14·1% (21·6; 16)	63·4% (24·0; 10)	29·6% (38·2; 7)
Continued dialysis ≥12 months†				
Pooled	1598/3560 (45%; 13)	19/1472 (1%; 6)	1579/2088 (76%; 7)	3/6 (50%; 1)
Individual studies	36·4% (38·3; 13)	1·5% (2·3; 6)	66·3% (25·8; 7)	No data
Recovery of enough renal function to come off dialysis				
Pooled	34/1765 (2%; 9)	5/64 (8%; 3)	29/1701 (2%; 6)	2/20 (10%; 3)
Individual studies	4·9% (7·1; 9)	7·3% (12·6; 3)	3·7% (3·4; 6)	22·2% (38·5; 3)
Transplant received				
Pooled	2321/16 608 (14%; 24)	41/4483 (1%; 11)	2280/12 125 (19%; 13)	71/381 (19%; 9)
Individual studies	6·3% (8·4; 24)	1·7% (1·3; 11)	10·3% (9·9; 13)	19·0% (26·6; 9)

Data are n/N (%; number of studies) or mean (SD; number of studies). NA=not applicable. *Countries reporting dialysis duration ≥3 months: Burkina Faso, Cameroon, Democratic Republic of the Congo, Ethiopia, Ghana, Malawi, Nigeria, Senegal, South Africa, and Sudan. †Countries reporting dialysis duration ≥12 months: Cameroon, Ethiopia, Ghana, Nigeria, Senegal, South Africa, Sudan.

Table 2: **Renal replacement therapy for end-stage kidney disease**

Leading causes of death were uraemia, volume overload (ie, too much water in their bodies that they could not excrete because of kidney failure), hypertension, discontinuation of dialysis, no vascular access, heart failure, stroke, or infections.[20–26]

Overall pooled mortality among patients with ESKD who received dialysis was similar among adults (1302 [31%] of 4228; 25 studies) and children (90 [32%] of 284; ten studies), but was higher among adults with incident ESKD (822 [80%] of 1031; seven studies) compared with prevalent ESKD (480 [15%] of 3197; 18 studies; table 3). Among patients who needed but did not receive dialysis, pooled known and presumed mortality was similar in adults (390 [96%] of 406; three studies) and children (133 [95%] of 140; nine studies). Among adults with incident ESKD, the difference in known and presumed mortality between those who did and did not receive dialysis was small (2747 [88%] of 3122, 14 studies *vs* 390 [96%] of 406; three studies). When South Africa and Sudan were excluded from the analyses, pooled mortality among adults and children who received dialysis increased further (appendix p 14). Pooled known and presumed mortality was similar between adult patients with prevalent ESKD who received peritoneal dialysis (121 [19%] of 650; seven studies) or haemodialysis (301 [16%] of 1884; nine studies; appendix p 15).

15 adult studies reported use of intravenous iron or erythropoietin for renal anaemia (appendix p 16). Access to both drugs was scarce, leaving patients mainly reliant on blood transfusions (mean 61·5% [SD 15·2]; six studies). Use of any intravenous iron (1870 [65%] of 2898; three studies *vs* 30 [25%] of 120; one study) or erythropoietin (2425 [74%] of 3287; nine studies *vs* 65 [19%] of 348; three studies) was higher in prevalent versus incident cohorts. Means of individual study proportions were generally lower than pooled proportions. One paediatric study reported use of erythropoietin for less than 1 week in two of 24 children and blood transfusion in five of 25 children.[27] Use of phosphate binders was reported in two of 42 and 19 of 45 patients in two adult studies.[28,29] Haemodialysis vascular access was described in 22 adult studies. Overall, the mean proportion of patients with arteriovenous fistula was 15·6% [SD 9·7] at the start of dialysis, but rose among prevalent patients over time (from 16·5% [10·9] to 61·3% [26·2]; appendix p 16). No study described regular laboratory monitoring. Four studies reported use of four 2 L exchanges daily for continuous ambulatory peritoneal dialysis (usual dose), and one study described use of a peritoneal dialysis cycler.[30–33] Frequency of haemodialysis was described in 17 studies (figure 2).[12,24,26,34–47] Most patients with prevalent ESKD received two 4 h sessions per week, but some received dialysis

	Adult studies			Paediatric studies
	Overall	Incident	Prevalent	
Known and presumed mortality*				
Pooled	5128/9057 (57%; 39)	4632/5860 (79%; 21)	496/3197 (16%; 18)	266/426 (62%; 11)
Individual studies	53·0% (34·0; 39)	79·6% (19·0; 21)	21·9% (15·9; 18)	70·4% (29·8; 11)
Mortality without dialysis although indicated				
Known†				
Pooled	NA	185/212 (87%; 2)	NA	43/51 (84%; 4)
Individual studies	NA	80·1% (13·1; 2)	NA	81·7% (15·8; 4)
Known and presumed*				
Pooled	NA	390/406 (96%; 3)	NA	133/140 (95%; 9)
Individual studies	NA	95·6% (7·6; 3)	NA	96·2% (8·0; 9)
Mortality with dialysis				
Known†				
Pooled	1302/4228 (31%; 25)	822/1031 (80%; 7)	480/3197 (15%; 18)	90/284 (32%; 10)
Individual studies	32·1% (27·1; 25)	60·0% (31·0; 7)	21·2% (15·7; 18)	50·5% (32·2; 10)
Known and presumed*				
Pooled	3243/6319 (51%; 32)	2747/3122 (88%; 14)	496/3197 (16%; 18)	107/294 (36%; 10)
Individual studies	48·7% (35·3; 32)	83·0% (19·4; 14)	21·9% (15·9; 18)	57·3% (35·1; 10)
Left hospital against medical advice, pooled	ND	ND	ND	27/143 (19%; 3)
Lost to follow-up, pooled	557/3087 (18%; 12)	443/1633 (27%; 7)	114/1454 (8%; 5)	188/675 (28%; 8)

Data are n/N (%; number of studies) or mean (SD; number of studies). NA=not applicable. ND=no data. *Patients with end-stage kidney disease who were known to have died plus those who left hospital against medical advice, were lost to follow-up, or stopped dialysis although indicated and therefore are presumed to have died without further treatment. †Patients known to have died.

Table 3: **Mortality in children and adults with end-stage kidney disease**

intermittently as resources permitted. Eight adult studies reported monitoring of dialysis adequacy, which was infrequent and often suboptimum (appendix p 17). The delivered dialysis dose tended to be higher among those receiving peritoneal dialysis than haemodialysis.

Nine adult and three paediatric studies described recovery of enough renal function for patients to discontinue dialysis. In pooled analyses, five of 64 adults with incident ESKD (8%; three studies) and two of 20 children (10%; three studies) came off dialysis (table 2). 2321 of 16 608 adults (14%; 24 studies) and 71 of 381 children (19%; nine studies) received a kidney transplant. A transplant was received by more adults with prevalent than with incident ESKD (2280 [19%] of 12 125 *vs* 41 [1%] of 4483). Transplantations were often done outside the country (data not shown). When studies from South Africa and Sudan were excluded, the proportion of patients receiving a transplant decreased substantially, to 54 (1%) of 4808 adults and four (3%) of 158 children (appendix p 13).

Discussion

The public health impact of ESKD does not lie exclusively in the numbers of patients affected, but also in the diagnostic and therapeutic challenges of management, which impose a substantial burden on individuals and the health system in resource-limited settings. So far, mostly single-centre studies have highlighted the local challenges in management of ESKD in sub-Saharan Africa. In this systematic review, we show that, even among the few people who reach a diagnosis of ESKD in sub-Saharan Africa, presumed and known mortality among adults and children was high, and was over 95% when patients were unable to access dialysis. Among patients who did start dialysis, mortality remained high, largely because of late presentation, frequent dialysis discontinuation, and suboptimum dialysis quality. Overall, only around 10% of adults with incident ESKD and 35% of children remained on dialysis for at least 3 months. Worldwide, higher mortality is noted within the first 120 days of starting dialysis compared with later months, which is largely attributed to comorbid illness, patient age, withdrawal from dialysis, or poor care before dialysis.[48] Although some of these criteria might explain the differences in mortality between patients with incident versus prevalent ESKD in sub-Saharan Africa, the attrition described in most studies was a result of the inability to pay for dialysis, occurring usually within the first 2 weeks of initiation (mean cost US$100–150 per haemodialysis session).[24,49] The adult ESKD population in sub-Saharan Africa tends to be young with few comorbidities; therefore, when patients do manage to pay for long-term dialysis, even though dialysis quality might be suboptimal, outcomes are much improved, with over 75% of patients with prevalent ESKD remaining on dialysis for over 1 year. Outcomes in children were generally between those noted

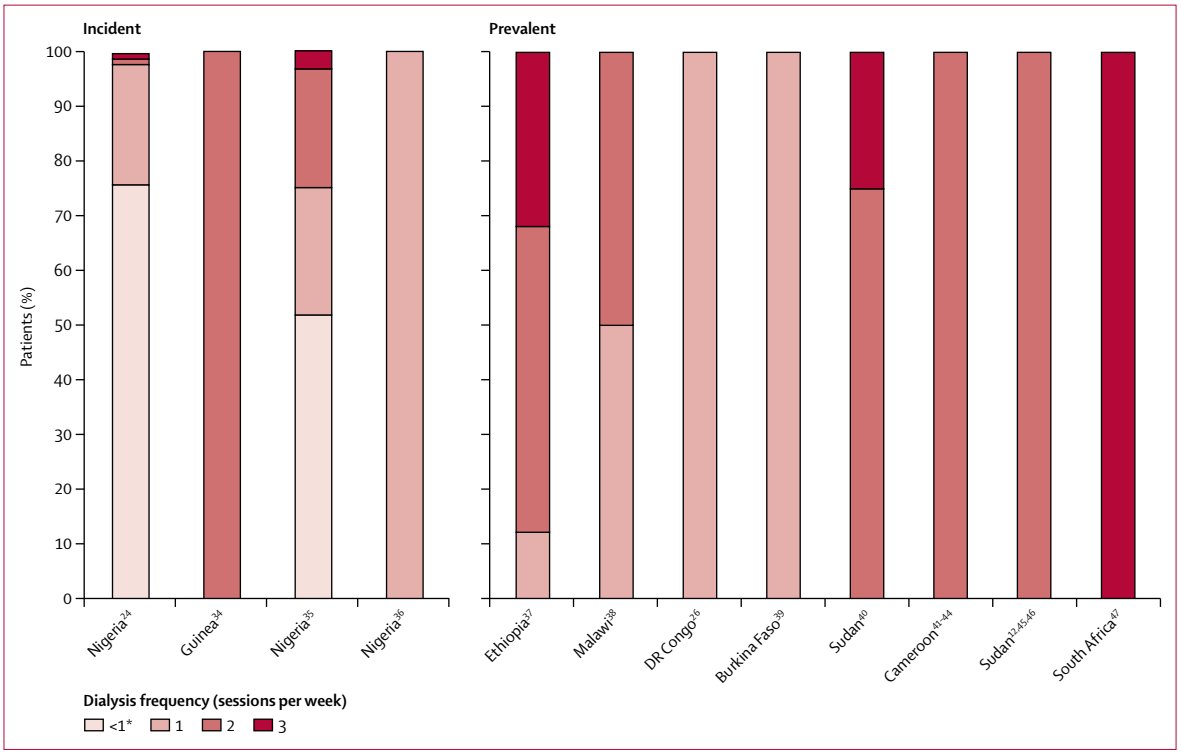

Figure 2: **Proportion of dialysis sessions received per week in incident and prevalent haemodialysis populations by country**
The standard haemodialysis dose is three sessions of 4 h per week, but varied in some studies. Each column represents data from one study or country; studies from the same country are shown separately when the dialysis frequencies differed. *Ranged from one dialysis session only to one session every 2 weeks to 2 months.

for adults with incident and prevalent ESKD; however, a high proportion of children left hospital against medical advice, suggesting that families make affordability decisions soon after diagnosis and there is little long-term dialysis available for children outside of South Africa and Sudan. Prospective studies are needed to identify differences in causes of death, reasons for dialysis discontinuation, and factors associated with dialysis continuation among patients with incident and prevalent ESKD and in children with ESKD in sub-Saharan Africa, to inform clinical decision making and policy development around ESKD care.

This systematic review complements our recent review on the outcomes of patients with acute kidney injury in sub-Saharan Africa, where access to dialysis and survival were also low.[17] The numbers of patients with acute kidney injury and ESKD who remain undiagnosed are unknown. Both reviews show that, even among patients who have resources to reach a diagnosis of kidney failure, dialysis is largely out of reach. Much attention has been focused recently on the diagnosis and management (including dialysis) of acute kidney injury because this disorder is less costly than ESKD.[50] Although this strategy might be efficient, this narrow focus raises equity questions for patients with other kidney diseases. Awareness must be raised about the plight of all patients with kidney failure in sub-Saharan Africa.

Recent publications have estimated the large unmet need for dialysis and a systematic review addressed the scarcity of trained staff in sub-Saharan Africa.[5,6,51–55] Where dialysis is available, even where partial government subsidies exist, many patients stop treatment and die once their resources are depleted because vascular access, laboratory and radiological testing, drug treatment, or transportation are not covered.[33,38,41,56,57] Such high attrition rates raise ethical questions about offering patients dialysis when their resources are known to be inadequate to sustain treatment. However, some patients, being fully informed, still wish to try. In countries where full dialysis costs are covered by the government, although individual outcomes are improved, access is still limited by official rationing (South Africa), out-of-pocket costs needed for transportation and drugs (Sudan), and insufficient dialysis infrastructure to treat all those in need.[11,12,22,31]

The quality of dialysis delivered is also resource-dependent, and many patients cannot afford, or dialysis centres cannot provide, regular dialysis. Dialysis quality, as measured by use of erythropoiesis-stimulating drugs; permanent vascular access; dialysis dose; dialysis adequacy; and access to transplantation, was poor even among those able to afford long-term dialysis. One study[35] described repeated femoral vein catheterisation as the predominant form of dialysis access in 105 of

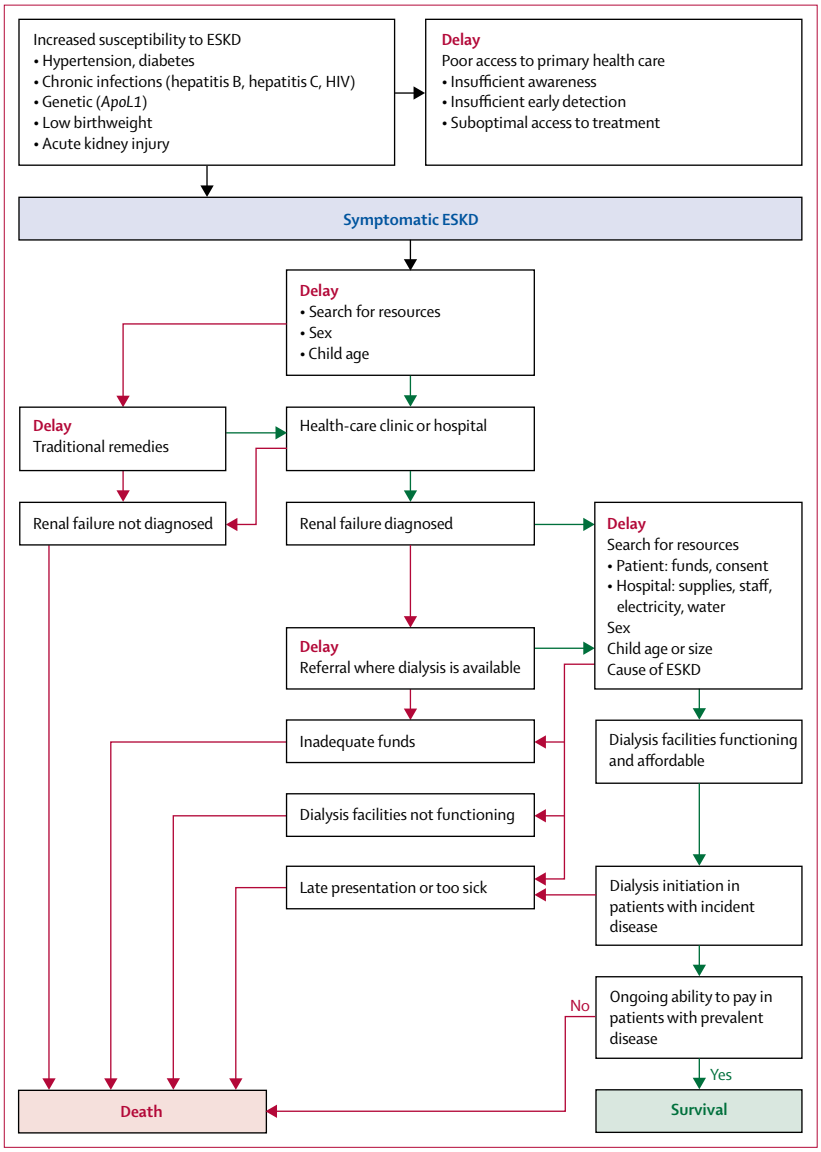

Figure 3: **Barriers to care in end-stage kidney disease**
Flow diagram showing barriers in access to dialysis contributing to mortality in ESKD in many sub-Saharan African countries. Green arrows show factors present to facilitate diagnosis of ESKD or referral for or access to dialysis; red arrows show absence of these factors. Most barriers are related to access to care, access to diagnosis, out-of-pocket payments needed, and infrastructural resources. ESKD=end-stage kidney disease. Figure adapted from Olowu and colleagues.[17]

120 patients because of cost. Measurement of dialysis adequacy was rarely reported. However, when measured in Sudan, a proportion of patients achieved target adequacy despite the lower haemodialysis dose, and dialysis quality might be better with peritoneal dialysis under the circumstances.[12,45] This finding should provide a rationale to advocate more affordable peritoneal dialysis for ESKD.[10,33,58]

Common barriers contributing to mortality in ESKD in sub-Saharan Africa are shown in figure 3. The most common patient barriers to accessing dialysis and achieving adequate dialysis quality are the unaffordable costs of dialysis, transportation, drug treatment, vascular access, and transplantation workup.[12,29,35,49] In view of the unexpected low prevalence of HIV as a cause of ESKD, some underlying diseases and comorbid conditions might also represent barriers.[11,49,59] Female sex is a systematic barrier to access to ESKD care in sub-Saharan Africa.[60] In the reviewed studies, young children were under-represented, potentially because of unwillingness to pay and paucity of facilities for infants.[61] Infrastructural barriers include the scarcity of dialysis facilities, which when available are predominantly in urban centres, might be dependent on donated outdated equipment that cannot be maintained, are often affected by staff and stock shortages, and cannot meet the clinical need.[33,38,62,63] Identification of common barriers occurring in daily practice is important to stimulate debate about pragmatic approaches to prevention, diagnosis, and management of ESKD in sub-Saharan Africa.

This systematic review has important limitations and several strengths. In view of the scarcity of high-quality studies, all papers were included in an attempt to reduce further bias by exclusion. The diagnosis of ESKD was not uniform across studies and in view of the clinical circumstances in much of sub-Saharan Africa, the distinction between acute kidney injury and ESKD was not always possible. Therefore, some patients with acute kidney injury might have been incorrectly diagnosed as having ESKD. Erroneous inclusion of patients with acute kidney injury could have biased the outcomes towards underestimation of mortality in ESKD, especially among adults with incident ESKD. Not all studies reported on all outcomes; therefore, denominators vary for each analysis, but the data presented represent the best available and patient numbers are high, which are important strengths. The finding that about 40–50% of patients in the identified studies received dialysis at least once is probably a substantial overestimate of the true figure, as reported in 2015.[6] Almost all studies were from centres with dialysis facilities and therefore represent only patients who received a diagnosis of ESKD and had reached a dialysis unit. Thus, publication bias exists in terms of access to dialysis, but outcomes reported remain relevant. The outcomes and dialysis quality measures are poor and represent the daily reality of dialysis practice in many countries in sub-Saharan Africa. Dialysis duration and mortality rates were reported with varying follow-up times in individual studies. However, we believe that the small proportions of patients remaining on long-term dialysis is probably a valid indirect indicator of dialysis duration and high early mortality in patients with ESKD. Differences between pooled proportions and means of individual study frequencies for some outcomes show variability between studies. These differences are likely to reflect differences in study size, but also probably reflect many other factors such as local logistics, infrastructure, skill, geographical location, and distribution of poverty or affluence of patients included,

which will have affected study outcomes. The overall heterogeneity of the data emphasises the urgent need for good systematic data collection on incidence and prevalence of ESKD as well as the need to perform and publish higher quality studies in the region. Despite the data only representing 15 countries in sub-Saharan Africa, the consistency of problems encountered and poor patient outcomes across studies suggest generalisability of these findings. Despite the inherent limitations, this systematic review provides important insights to encourage and inform policy development and health-system-wide planning to address ESKD in sub-Saharan Africa.

Dialysis facilities and dialysis populations are expanding in sub-Saharan Africa.[15] The consequences for the individual, in terms of catastrophic expenditure and life or death, and for the health system, in terms of opportunity costs and equity, cannot be ignored. Few countries in sub-Saharan Africa have official policies for renal replacement therapy, and some governments are reluctant to broach the debate about coverage of renal replacement therapy, which is fraught with ethical dilemmas. Without formalised criteria or official guidelines, access to dialysis is haphazard, often depending on luck if facilities are available, and ability to pay. The burden of so-called choice between life and death is shifted to individual clinicians, patients, and families, imposing substantial moral distress.[64] However, before development of ESKD policies, existing knowledge gaps about the local burden of disease, outcomes, assessment of current treatment capacity, and the socioeconomic implications of kidney disease must be filled.[65] Engaging in public debate about the justice implications of starting expensive programmes such as dialysis, which deliver acceptable quality care, in environments where opportunity costs are likely to be very high is important to develop sustainable and equitable solutions for patients with kidney disease.

Contributors

GA reviewed and scored articles, planned the study, analysed data, and wrote the manuscript. CO, WAO, and AN reviewed and scored articles, planned the study, and reviewed and revised the manuscript. FA did the literature search, reviewed and scored articles, planned the study, and reviewed and revised the manuscript. JP and SN planned the study and reviewed and revised the manuscript. VAL did the literature search, reviewed and scored articles, planned the study, analysed data, and wrote the manuscript.

Declaration of interests

We declare no competing interests.

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Interpretation: The studies reported in *Papers 1 and 2* were the first systematic reviews to be conducted on dialysis outcomes in SSA. Systematic reviews are regarded as one of the higher forms of data reliability, although they are highly dependent on the quality of studies that are included. In total 109 studies, including a total of 27 879 patients from 20 countries, reported over 25 years, were identified and reviewed. Strikingly, there were far fewer patients reported on with AKI (3340 patients) compared with ESKD (25 265 patients). Two thirds of the ESKD patients were from Sudan or South Africa, however, where governments provide substantial support for chronic dialysis. Children were more represented in the AKI studies (1572 children, 1042 adults) than in the ESKD studies which overwhelmingly included adults (809 children, 24456 adults). These observations highlight the additional barriers to care for children with ESKD in SSA, where families can rarely afford to pay for long-term dialysis and facilities are very sparse.

Almost all studies were of low to medium quality, which reflects the resources available for research in SSA. Despite this, given that these studies comprised the only existing data at the time, the studies were all included in the analyses and data was presented as thoroughly and transparently as possible. Given the large heterogeneity of data presented across all the studies, statistical analysis was limited. The reviewers of *Paper 1* initially requested a meta-analysis, which we did perform and included in our response letter to the reviewers, however we strongly emphasized not wanting to give a false sense of data robustness and our preference not to include this in the manuscript. The reviewers agreed. In seeming contrast, the reviewers of *Paper 2* requested removal of even the simple descriptive statistics from the manuscript as they felt the large discrepancies in outcomes between patient groups were self-explanatory. An important strength of these systematic reviews is that they combine data from adult and pediatric cohorts and are therefore as generalizable as possible to the population of patients who are diagnosed with kidney failure requiring dialysis in SSA. A major weakness of the reviews is that they very likely reflect publication bias, represent only patients who were able to access some level of care, where a diagnosis of either AKI or ESKD was made and dialysis was considered. How great the proportion of patients remaining undiagnosed and never reaching a possibility of dialysis remains unknown. As such these systematic reviews likely represent a more privileged segment of patients, which makes the poor outcomes observed even more concerning.

Overall, the access to dialysis in SSA is currently low and the outcomes of patients with both AKI and ESKD are poor compared with world outcomes as summarized in Table 3.

Table 3: Summary of outcome data among patients requiring dialysis in SSA (*Papers 1 and 2*)

	Acute kidney injury		End-stage Kidney Disease		
	Adults	**Children**	**Incident adults**	**Prevalent adults**	**Children**
Patient number	1043	1937	10354	14102	809
Mortality without dialysis when needed	86%	73%	96%	NA	95%
Mortality with dialysis#	30%	30%	88%	16%	36%
World mortality*	*24%*	*14%*	*15-30 deaths/100 patient years (1^{st} 120 days)*	*41-60% (at 5 years)*	*15.8 deaths/1000 patient years (at 5 years)*
Remained on dialysis at 12 months	–	–	1%	76%	50% (1 study, 3 of 6 patients)
Patients transplanted	–	–	1.3%	19%	19%
Left against medical advice or lost to follow up	12%	9%	27%	8%	26%

NA – not applicable. Incident adults – adults with new diagnosis of ESKD; Prevalent adults – adults established on chronic dialysis for > 3 months. Table compiled from references[65,66] and *World data compiled from[67-69]; # Follow-up time variable, rarely > 1 year.

Most patients with kidney failure in SSA likely remain undiagnosed and die at home. Of those who do reach a hospital with some form of kidney care, most patients die within days to weeks or disappear, being unable to access or sustain the costs of ongoing dialysis. Among patients who do manage to sustain chronic dialysis over the long term, outcomes are far superior demonstrating that once dialysis is accessed sustainably patients in SSA can thrive, especially as they often have few co-morbidities when compared to patients in higher income settings. Such patients however currently represent a very privileged minority in SSA. Access to kidney care is therefore highly inequitable across SAA. This needs to be acknowledged by policy makers and consideration must be given to potential equitable solutions.

CHAPTER 2. Moral distress among nephrologists in sub-Saharan Africa

Given the lack of policy clarity around provision of dialysis and who should gain access, decisions are most likely made on a case-by-case basis if and when a patient reaches a center where kidney disease is diagnosed and dialysis may be a possibility. The International Society of Nephrology (ISN) has been engaged in various capacity building activities over the past 2 decades and has provided varying degrees of training to close to 900 fellows in nephrology from LMICs, including many from SSA, most of whom have returned to their home institutions.[70] A recent survey reported that the number of nephrologists in SSA has increased from 218 in 17 countries in 2008 (70 and 55 working in Nigeria and South Africa respectively) to 539 in 36 countries in 2015 (162 and 108 in Nigeria and South Africa respectively).[29] A critical mass of nephrologists is therefore accumulating in SSA with knowledge on how to manage patients across the spectrum of kidney disease. The resources on the ground however, especially in the public sector, have not kept pace with the training. It is conceivable that this mismatch leads to frustration and distress among nephrologists.

As identified in the 2 systematic reviews presented in Chapter 1, because of low awareness in the community, pervasive poverty and lack of access to primary care, patients with kidney disease tend to present very late and are often close to death. Delays imposed by transportation, searching for funds and poorly functional or insufficient infrastructure may lead to death before dialysis can be initiated even if it would have been possible (as illustrated in *Figure 3, Paper 2*). In other cases, when patients are extremely poor, the option of dialysis may not even be presented to them as the nephrologists and nurses feel the consequences for the family would be too severe. How the principles of biomedical ethics in terms of respect for patient autonomy, beneficence and non-maleficence play out in these scenarios is highly complex as the ramifications of individual decisions extend to families and communities. There is a dearth of literature on the health care worker perspectives in nephrology from SSA. A pilot survey was therefore conducted to investigate barriers to dialysis and their impact on physician moral distress. The results of this survey are highlighted in *Presentation 1*.

Presentation 1: MORAL DILEMMAS ENCOUNTERED BY PHYSICIANS TREATING PATIENTS WITH KIDNEY DISEASE IN SUB- SAHARAN AFRICA HIGHLIGHT THE NEED FOR TRANSPARENT PRIORITY SETTING

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Background: Two recent systematic reviews have highlighted the plight of patients with kidney disease in sub-Saharan Africa (SSA) when they require costly therapy for survival.[65,66] Among patients with acute kidney injury (AKI), mortality was 73% in children and 86% in adults who required, but could not access, dialysis. Among adult patients with end-stage kidney disease (ESKD) who did begin dialysis, 84% discontinued this life-sustaining treatment largely because of unaffordable out-of-pocket costs. Physicians meet these patients daily and have first-hand information on how decisions are made and how resources are distributed. The role and experiences of health workers treating these patients in SSA have however not been well explored.

Aim: The aim of this study was to get an overview of the challenges faced on a daily basis by physicians in SSA who manage patients who require dialysis. Our specific focus was to investigate if and how physicians handle bedside rationing situations.

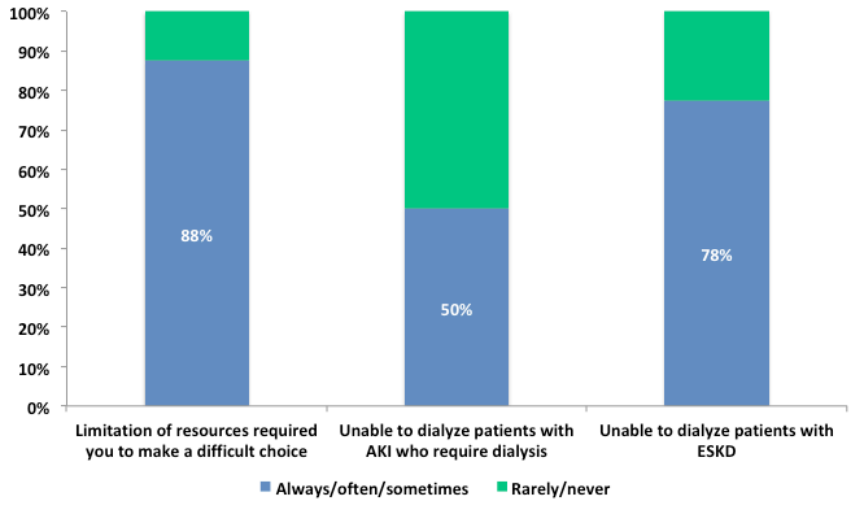
Methods: A survey was conducted among a randomly selected group of nephrologists in SSA. The questionnaire was developed, partly based on a previously validated survey instrument used among physicians in Ethiopia[71] and questions were asked about the frequency of specific experiences within the 2 years prior to the survey. Paper copies of the survey in English and French (the 2 official languages of the African Association of Nephrology, AFRAN) were distributed and collected at the AFRAN and the Kenyan Renal Association (KRA) meetings in 2017. At the AFRAN meeting 80 surveys were distributed in the conference bags for attendees, 20 surveys were distributed at the KRA meeting. Survey participation was voluntary and

anonymous. Formal ethics approval was deemed not required by the Cantonal Ethics Committee of Zürich. Survey responses were manually entered into Survey Monkey for analysis.

Results: Thirty-nine completed responses were received. Of the respondents, 80% were male, 61% were aged 36-55 years and 74% had been in medical practice >10 years. Respondents represented 15 countries in sub-Saharan Africa. Most respondents worked in government and/or teaching hospitals (62%) in addition to private practice (32%). Ten percent of respondents managed patients under 18 years of age.

The participants frequently saw patients in need of dialysis, though fewer patients were initiated on dialysis: 34% of respondents saw > 5 patients who required dialysis for AKI and 69% saw > 5 patients with ESKD per week, but 75% and 54% of respondents reported that <5 patients per week were initiated on dialysis for AKI or ESKD respectively. Overall 50% and 78% responded that within the last 2 years they had frequently (always, often or sometimes) been unable to dialyze a patient with AKI or ESKD respectively (Figure 1).

Figure 1. Inability to provide dialysis when required



Concerns regarding high out-of-pocket expenses were reported by the majority of the physicians. While 84% of respondents were concerned that laboratory testing was unaffordable to the patient often or sometimes, 82% were concerned that medication was unaffordable

(Figure 2), 89% felt pressured by the patients' financial constraints and 84% felt pressured by the institution's financial restraints (Figure 3). Overall 85% reported the preferred course of treatment was not pursued because of costs (Figure 3).

Figure 2. Concern over cost limiting laboratory testing and medications

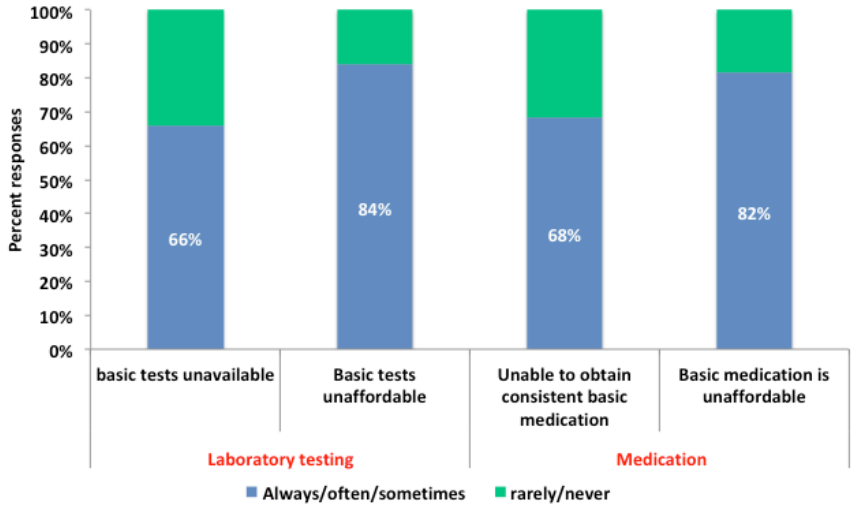
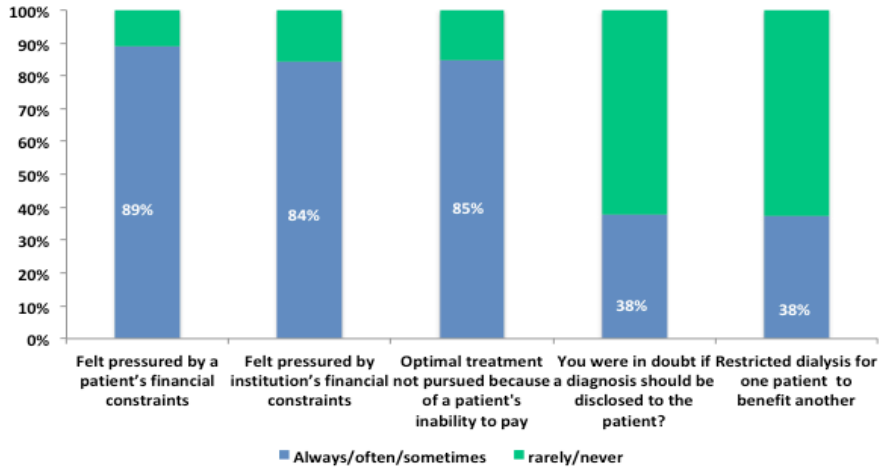
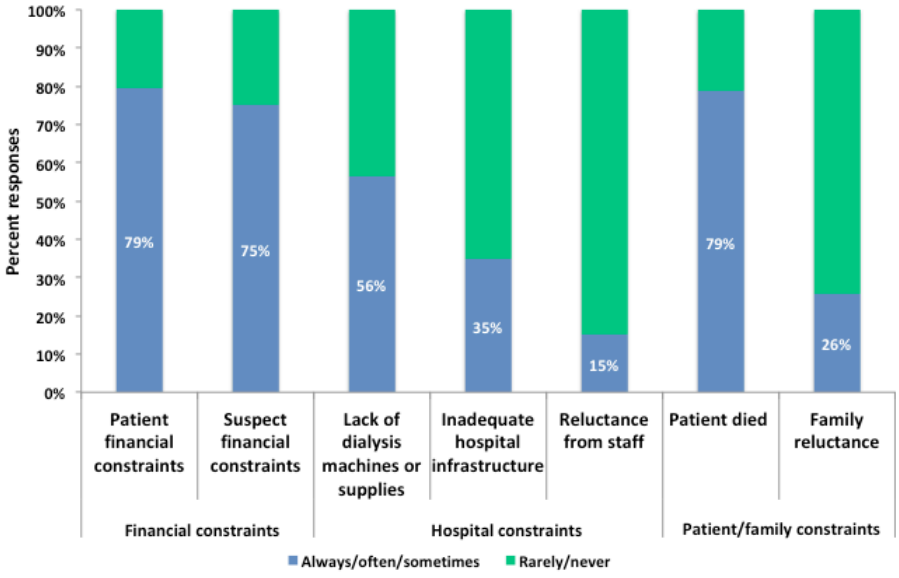


Figure 3. Felt pressure because of patient/institutional financial restraints



Almost 40% of physicians reported having to make difficult decisions regarding disclosure of the diagnosis to a patient and having to restrict dialysis for one patient because another patient needed it more (Figure 3). Often or always most respondents experienced inability to initiate dialysis because the patient admitted financial constraints (67%), dialysis machines or supplies were lacking (56%) or the patient died before dialysis could be started (79%) (Figure 4).

Figure 4. Barriers to provision of dialysis

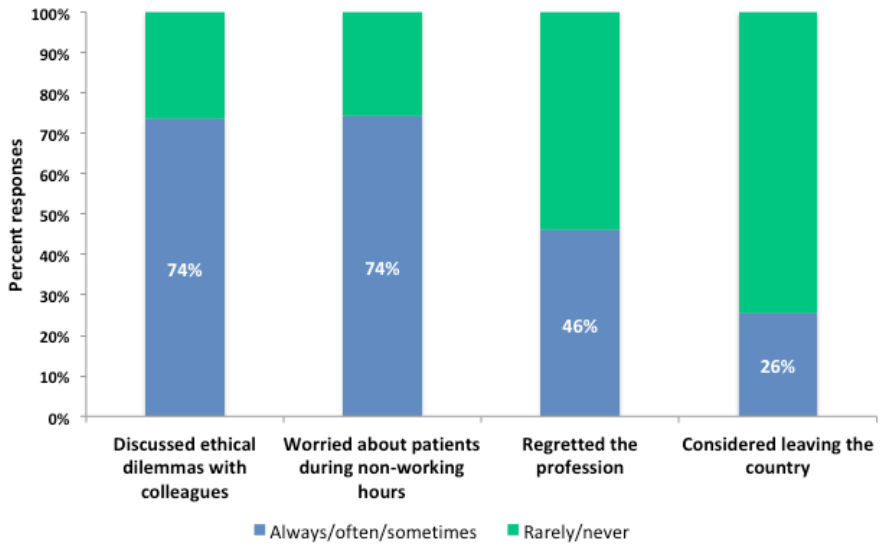


Around 75% of respondents reported that patients at least sometimes reduced dialysis frequency and/or used temporary catheters instead of permanent vascular access to reduce dialysis costs. Ninety-five percent of physicians agreed or somewhat agreed that they have seen patients plunged into financial crisis as a result of health care costs. Three of four nephrologists were burdened by ethics dilemmas and worried about patients out of hospital hours (Figure 5). As a consequence almost half of physicians surveyed regretted their choice of profession and a quarter considered leaving the country.

In the free text responses many physicians expressed concern over patients' inability to pay for needed care. Many felt unsupported by their governments given the absence of resources and the absence of guidance in terms of dialysis resource allocation. Pressure from families to

initiate dialysis was also cited as a source of stress, especially when patients were referred very late or had other irreversible comorbidities.

Figure 5. Personal conflict about provision of care



Conclusions: Physicians managing patients with kidney failure in SSA frequently face resource scarcity and ethical dilemmas due to patients' inability to pay. The level of moral distress among nephrologists is high, but when compared to the findings of the Ethiopian study[71] among general physicians, where 74% regretted their choice of profession at least monthly, the level appears lower. This finding could be interpreted in multiple ways: it is possible that specialists are relatively shielded from many of the every-day resource restraints experienced by generalists, more senior physicians (specialists) may have recourse to more resources especially if they also have private practices, more senior physicians may have become used to the resource limitations and develop a more fatalistic attitude, or specialists feel a sense of purpose and in the current climate where dialysis services and professional groups are expanding there may be a sense of hope for the future. The current study was conducted in a small sample and can only provide a glimpse into the real-world challenges patients and providers are dealing with on a frequent basis when dialysis exists but is not accessible in resource-deprived settings. The findings require further validation and study in diverse environments.

Interpretation: The sample of nephrologists surveyed here was small (response rate around 40%) which is a potential limitation that must be considered. Given that surveys were distributed in conference bags, together with other leaflets it is possible that some attendees did not recognize the survey for what it was. Planned participant information about the survey and requests for participation during the plenary session did not occur. It may therefore be likely that the results reflect a "positive" selection bias in terms of physicians who experience moral distress and felt the need to take the opportunity to express this. The low participant rate in contrast may reflect a lack of willingness to discuss or consider ethical dilemmas or that these issues are not perceived as important problems. An important strength of the survey, however, is it's voluntary nature and that it was anonymous, therefore increasing the likelihood that responses were truthful. Given the relative consistency of responses, in general a high or low percentage per response was obtained (few responses were around 50%), it is likely that the responses are representative of common ethical dilemmas experienced in nephrology practice in SSA. The clear dependence of the ability to provide care on a patient's resources is an important concern that must be addressed if moral distress is to be reduced and equity of access to dialysis is to improve.

Survey responses also highlight the tension that physicians feel between limitations of the patient's resources and those of the institution, illustrating the conflicting role of physicians practicing in resource limited settings who cannot focus entirely on the patient at hand but must consider simultaneous needs of other (sicker? or more salvageable?) patients and the broader resource climate. Despite worrying about patients and ethical dilemmas out of hospital hours, most physicians did appear to have recourse to colleagues with whom they could discuss and work through these dilemmas. Most physicians articulate that guidance on resource allocation from health-care decision makers is required to improve transparency and reduce the burden currently on their shoulders of having to ration care on a case-by-case basis.

CHAPTER 3. Public health and multi-sectoral approaches to improving global kidney health

Access to appropriate care for those who need it is a common clinical dilemma for patients with kidney disease and physicians in SSA. Given the current high costs, limited location and quality of infrastructure, and insufficient trained staff required to deliver equitable and sustainable RRT in SSA, it will take time until all the necessary building blocks are in place to be able to provide universal access to such care. Even in high-income settings, the costs of RRT are disproportionately high relative to the numbers of patients affected, however given the lifesaving nature of RRT and the lack of alternative treatments for kidney failure, these costs have been accepted by society. The demand for RRT is however rising globally, in part because of population aging, but also because of increased awareness and diagnosis. A general problem world-wide is that kidney disease is asymptomatic in the early stages and therefore tends to be diagnosed relatively late unless actively screened for.

Importantly, major risk factors for kidney disease, both acute and chronic, include structural factors such as poverty, unsafe work, lack of education and gender inequality. Such factors have all been highlighted in 2015 by the United Nations as the Sustainable Development Goals (SDGs), which are important targets to secure overall well-being.[72] Multiple public health measures such as ensuring access to clean water, vaccinations, prevention of malaria and HIV, as well as reducing dietary salt, sugar and fat intake, tobacco consumption and improving physical activity would all go a long way towards reducing the risk of both AKI and CKD/ESKD, even before access to the formal health system would be required. If kidney disease is diagnosed early, AKI can be reversed and the progression of CKD can be slowed with appropriate cheap interventions. Prevention, early diagnosis and early treatment of kidney disease would reduce the need for dialysis and transplantation and would therefore appear the most cost-effective long-term approach to the management of kidney disease. Not all kidney failure can be prevented, however, therefore strategies must be in place to provide RRT when required, but this should not be the only default strategy (as is currently occurring in much of SSA). A balanced approach to equitable management across the spectrum of kidney care is required.

Consistent with a coherent and comprehensive approach to maintaining kidney health and treating kidney disease, two papers highlighting potential public health approaches to the reduction of risk factors for kidney disease, with emphasis on LMIC (*Paper 3*) and how achievement of each SDG would have relevance for kidney health (*Paper 4*) were developed in collaboration with leading global nephrologists, as advocacy tools to complement the broader discussion around equity in access to kidney care.

PAPER 3

REDUCING MAJOR RISK FACTORS FOR CHRONIC KIDNEY DISEASE

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Reducing major risk factors for chronic kidney disease

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Chronic kidney disease (CKD) is a global public health concern and a key determinant of poor health outcomes. While the burden of CKD is reasonably well defined in developed countries, increasing evidence indicates that the CKD burden may be even greater in developing countries. Diabetes, hypertension, and obesity are major contributors to the global burden of the disease and are important *traditional* CKD risk factors; however, *nontraditional* CKD risk factors such as nephrotoxin exposure, kidney stones, fetal and maternal factors, infections, environmental factors, and acute kidney injury are also increasingly being recognized as major threats to global kidney health. A broad approach to CKD prevention begins with the identification of CKD risk factors in the population, followed by the development of appropriate mitigation strategies. Effective prevention policies rely on an accurate understanding of the incidence and prevalence of CKD in a given setting, as well as the distribution and burden of risk factors. Populations or individuals at CKD risk must be screened and treated early to prevent the onset of and delay the progression of the kidney disease. Systematically collected data should be analyzed at country, province, and district levels to identify regional disparities and CKD hotspots and develop targeted prevention strategies. Race-ethnicity, genetics, sex, socioeconomic status, and geography are likely modifiers of CKD risk. A comprehensive, informed approach to prevention that takes into account all of these factors is therefore required to successfully tackle the global CKD epidemic.

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Chronic kidney disease (CKD) is increasingly recognized as a global public health concern and an important contributor to morbidity and mortality.[1] While the burden of CKD is reasonably well defined in developed countries, increasing evidence indicates that the CKD burden may be even greater in developing countries.[1,2] Of the major contributors to the global burden of disease, diabetes, hypertension, and obesity are *traditional* risk factors for CKD.[1] *Nontraditional* CKD risk factors such as nephrotoxins (e.g., prescription medicines and alternative remedies), kidney stones, fetal and maternal exposures, infections, environmental exposures, and acute kidney injury (AKI) are also being increasingly recognized as major threats to kidney health.[3] The burden of CKD that is attributable to nontraditional risk factors is unknown and may even predominate in low- and middle-income countries (LMICs).

A broad approach to CKD prevention begins with the identification of the incidence, prevalence, and distribution of

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risk factors, followed by the development of mitigation strategies. At-risk populations or individuals must be screened and treated early to prevent onset and delay progression. Reducing CKD risk is also highly dependent on addressing the fact that it is both a consequence of and a contributor to socioeconomic disparities. This review expands on the recently published International Society of Nephrology (ISN) CKD roadmap,[4] which discusses the globally relevant major traditional and nontraditional risk CKD factors (outlined in Table 1), highlights gaps in knowledge, and recommends strategies to close these gaps and enhance CKD prevention.

Prioritization of CKD and detection and investigation of CKD hotspots

To understand whether CKD is a priority within a country, incidence and prevalence, as well as the contribution of various risk factors for the burden of disease should be determined. Systematic and reliable data collection is required. It is important that such data are analyzed at region, country, province, and district levels to identify local disparities and CKD hotspots. For example, the global burden of disease study has identified several hotspots in Central America where the prevalence of CKD is high and requires attention.[5–7] These include Mexico, where women have one of the highest disability-adjusted life-year rates for CKD (related to obesity, diabetes, and hypertension), as well as pockets in Nicaragua, Guatemala, and El Salvador, where CKD of unspecified cause is highly prevalent in men, primarily related to nontraditional risk factors.[7,8]

To illustrate the importance of subregional local analysis, in Nicaragua, increased CKD rates in male farmers aged <60 years were associated with pesticide exposure, dehydration, alcohol consumption, and exposure to heavy metals.[9] Costa Rica has reported a higher incidence of CKD among young sugarcane workers, with clinical and histological findings of chronic interstitial nephritis.[10] In El Salvador, a high prevalence of CKD (17%) was observed among male farmers exposed to toxic pollutants.[11,12] Studies in Sri Lanka reported an association between pesticide poisoning and pollutants, with repeated episodes of AKI and CKD.[13] In India and Pakistan, a large percentage of CKD cases are of undetermined etiology, potentially related to environmental factors.[14] Many knowledge gaps remain regarding these regional epidemics of CKD of unspecified cause.[5]

Gaps. There are no reliable statistics about the prevalence of CKD in most of the developing world. Improving and expanding local data collection and processing and research infrastructure is recommended to ensure a better understanding of the burden and regional distribution of specific CKD risk factors.

Action strategies. Including screening for kidney disease in established noncommunicable disease (NCD) risk factor surveys will add significant value to existing efforts to monitor the prevalence of NCD risk factor, likely at a lower cost than duplicating efforts with parallel CKD surveillance programs. Combining such survey data with global positioning technology will permit the identification of regional and local variations in CKD occurrence. For example, the World Health Organization (WHO) STEPwise approach to surveillance is an NCD household survey that was launched in 2002.[15] To date, 122 countries have participated.[16] Depending on the local resources, the survey collects behavioral risk factors (step 1); physical measurements, including blood pressure (BP), height, and weight (step 2); and biochemical parameters (blood glucose and lipids; step 3).[17] Advocacy efforts in Uruguay succeeded in including serum creatinine and urine protein measurements in the STEPwise approach to surveillance survey in 2006. This effort captured the attention of policy makers and resulted in a policy mandating kidney disease screening in individuals with hypertension or diabetes at regular health checkups in the employed population. This program is raising CKD awareness and will permit tracking of prevention efforts.[18]

Importantly, surveillance or outreach activities must include vulnerable groups and ensure equitable representation of the population. Monitoring activities should integrate national data at regional and local levels with data obtained in research and screening activities to optimize efficiency, facilitate surveillance, and permit the rapid identification of geographic hotspots for CKD that require focused attention.[19] A task force supported by global experts should be setup to investigate hotspots rapidly. Investigations should include standardized data on social, structural, and clinical risk factors, clinical course, and potential interventions. A guideline-based approach should be disseminated and adapted in regions experiencing CKD hotspots. An example is the international study group on CKD of unspecified cause in Mesoamerica, organized by the Central American Program for Work, Environment, and Health.[20] Such efforts require a multi-sectoral approach with sustainable financing.[21]

Tackling CKD risk factors: diabetes, hypertension, and obesity

The WHO global action plan for the prevention and control of NCDs does not include CKD among the four priority NCDs. However, diabetes, hypertension, and cardiovascular disease (CVD) are acknowledged to be integrally linked with CKD. Notably, CKD is an important risk amplifier within these conditions.[22] Across the world, 415 million adults have diabetes, 1.4 billion adults have hypertension, and 2.1 billion children and adults are overweight or obese.[23–25] The prevalence of CKD in adults with type 2 diabetes is approximately 25% to 40%, depending on population factors.[26–28] In the United States, the prevalence of CKD is approximately 30% among adults with hypertension and 17% among obese adults.[26] The size of the population at CKD risk is influenced by regional differences in demographics, different approaches to diagnosis and management, and effectiveness of local interventions to address lifestyle-related risks. Reduction of lifestyle-related risks is a cornerstone of mitigating the public health impact of diabetes, hypertension, and obesity. There is clear evidence that links upstream factors such as poor diet, poverty, food insecurity, tobacco consumption, and other

Table 1 | Global relevance of major risk factors for chronic kidney disease and suggested mitigation strategies

Risk factor	Global prevalence	Primary prevention	Projected CKD risk	Secondary prevention of CKD	Knowledge gaps	Relevance for HIC	Relevancy for LIC	Advocacy required	Refs
Diabetes type 2	**All diabetes** 387 million with largest concentrations in Western Pacific (138 million) and Southeast Asia (75 million) **Type 2:** About 95% of overall global prevalence	Education, lifestyle, diet, exercise, weight management	~40% overall and >50% in most non-White populations	Glucose control, BP control, lifestyle factors (avoiding high dietary protein), ACEI, or ARB	Glucose targets, best medications, need for novel therapies for diabetic kidney disease	Obesity, DM, GDM	Increasing obesity and DM, GDM Poor facilities for diagnosis and treatment	Policy development around food content and prices of healthy food, urban planning to increase walking opportunities, tobacco UHC Access to diagnosis, reliable access to medication and lifestyle	37,42,43,59
Diabetes type 1	**Type 1:** About 5% of overall global prevalence	Viral exposure?	~30% not known to vary by race-ethnicity	Glucose control, BP control, lifestyle factors (avoiding high dietary protein), ACEI, or ARB	Glucose targets, novel therapies for diabetic kidney disease	Glycemic control	Glycemic control, poor facilities for diagnosis and treatment	UHC Access to diagnosis Reliable access to medication and lifestyle	37
Hypertension	2010: 31% of adults globally (28.5% in HIC, 31.5% LMIC) 1.39 billion people (349 million in HIC, 1.04 billion in LMIC)	Education, lifestyle, diet, exercise, weight management, smoking, stress reduction	~10%	BP control, ACEI, or ARB if high-level albuminuria, other medication types?	Albuminuria-based targets?	Obesity, dietary sodium	Obesity, dietary sodium, strokes also high Awareness, treatment, and control very low in LMIC	Policy development around food sodium content, tobacco, and alcohol Need to increase awareness, treatment, and control globally UHC Consider polypill strategy Awareness, access to diagnosis Reliable access to medication and lifestyle	23
Obesity (Risks may vary for childhood and adult obesity)	**Adult**: Overweight 2013: 36.9% men, 38.0% women Obesity 2014: 10.8% men,	Education, lifestyle, diet, exercise, weight management, stress reduction	Unknown proteinuria or macroalbuminuria present in 4%–10% obese patients In morbidly obese,	Diet, exercise, weight loss, bariatric surgery (HIC) ACEI or ARB for proteinuria	CKD risk optimal BMI and variance by race-ethnicity and age, safe and effective weight	Access to weight management programs	Access to weight management programs Social roots of obesity, namely poverty,	Policy development to regulate food content, food prices, urban planning	140,159–163

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Table 1| Global relevance of major risk factors for chronic kidney disease and suggested mitigation strategies (Continued)

Risk factor	Global prevalence	Primary prevention	Projected CKD risk	Secondary prevention of CKD	Knowledge gaps	Relevance for HIC	Relevancy for LIC	Advocacy required	Refs
	14.9% women **Children**: In 2014, 41 million children aged <5 yr were overweight or obese (48% in Asia, 25% in Africa)		risk of GFR decline of ≥30% over 4 yr was 48.2 per 1000 person-yr Adolescent obesity associated with HR of 6.9 for all ESKD and HR of 19.4 for diabetic ESKD		management strategies, namely bariatric surgery		culture, access to nutritious food	to permit physical exercise Access to better diet, education, physical activity education	
Medications (Antibiotics, NSAIDs, PPI, counterfeit drugs, contrast media)	AKI: 24% globally related to nephrotoxins (29% HIC, 22% UMIC, 23% LLMIC) CKD: Unknown	Improve awareness, prescription flagging, stop unnecessary prescriptions	70% of children with nephrotoxin-induced AKI had CKD at 6 mo CKD risk variable, by medication	Early detection, urine screening for leukocytes, stop medications early	Burden of disease Which medication may increase CKD risk	Electronic alert systems, prescription data-sharing databases, package warnings	Reduce counterfeit drugs, regulate drug manufacturers to reduce adulterants	Awareness, prescription practices, marketing	64,71,72
Traditional/ alternative remedies	Frequent use globally, >80% in LMIC	Improve awareness, improve access to alternatives (UHC)	35% of AKI in Africa Unknown contribution to CKD, increased risk of ESKD with consumption of some remedies	Stop medication, hydration	Burden of disease, toxic compounds	Huge market of OTC and over-the-Internet Need regulation of the industry	Engage with communities to understand reasons for use, barriers to western medicine, etc.	Policies to regulate manufacture and sale of alternative remedies, limit unfounded or fraudulent advertising UHC Awareness, collaboration with traditional healers, improve access to medical care or affordability of medication, encourage publication of case reports to build database	76,86,164
Kidney stones	Geographic variability Adults: 5%–9% Europe, 12% Canada, 13%–15% USA, 1%–5% East, 20% Saudi Arabia	Increase awareness of local risks, emphasize on the importance of hydration, certain infections	GFR tends to be reduced in stone formers vs. non–stone formers	Hydration, diet, recurrent stone prevention, early reversal of obstruction	Regional risks	High costs	Likely unrecognized important cause of CKD and infections	Access to clean water, reduce environmental or occupational risks Increase awareness of need for follow-up for CKD, CVD in stone formers	88,90,106

Low birth weight/SGA/ prematurity	Globally: LBW 15%, Preterm 10% In LMIC, 2010: 13.7 million babies preterm; 2010: 43.3 million babies LBW/ SGA	Avoid obesity, maintain healthy lifestyle	70% increased risk	Screen for BP and proteinuria Treat early	Would reduction impact future risk?	Increased maternal age, assisted reproduction, maternal chronic illness	Preeclampsia, maternal malnutrition, poverty, war, poor antenatal care, pregnancy spacing, child marriage	Awareness, public health care measures, optimize maternal and child health, avoid childhood obesity UHC Document birth weights, prematurity in health care record Need for long-term follow-up of children at risk	112,114
Preeclampsia/ eclampsia	2%–5% globally Global prevalence 2013: 1.3 million	Optimize maternal health prepregnancy	RR HT–3.7 RR microalbuminuria 4–8 RR ESKD 4.7 RR kidney biopsy 3.3	Screen for BP and proteinuria and treat early	How to diagnose and prevent?	Prematurity, later CVD, ESKD	Prematurity, CVD, ESKD	Maternal health Access to antenatal care UHC Mothers require long-term follow-up for CKD and CVD	124,145,165,166
HIV	2013: 35 million worldwide, 24.7 million in sub-Saharan Africa	Education, use of condoms	Africa: 6.0%–48.5%, Europe 3.5%–18%, Hong Kong 18%, Brazil 1.1%–5.6%, India 27%, Iran 20%	PEP, HAART	Impact of HAART on all forms of renal disease, other kidney diseases in HIV-infected individuals	Competing risks of mortality	Poverty, suboptimal access to ART, ongoing infection risk, ApoL1 genotype with African origin	Policies around needle sharing, prostitution UHC National policies for prevention education, access to ART, reduce gender and/or sexuality discrimination, empower women, surveillance of renal function on ART	134
Hepatitis B	Global prevalence 2013: 331.0 million	Education Reduce scarification Vaccination	Hepatitis B-associated GN: 3% France, 3% China	Treatment Hepatitis B	Impact of routine vaccination on CKD burden	Reduce HCC, liver failure transplant	High prevalence	Policies around needle sharing, vaccination Advocacy for sexual health, drug abuse Equity in access to vaccination.	145,146,149

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Table 1| Global relevance of major risk factors for chronic kidney disease and suggested mitigation strategies (Continued)

Risk factor	Global prevalence	Primary prevention	Projected CKD risk	Secondary prevention of CKD	Knowledge gaps	Relevance for HIC	Relevancy for LIC	Advocacy required	Refs
								(Vaccination reduced membranous nephropathy among Taiwanese children) Equity in access to antiviral therapy	
Hepatitis C	Global prevalence 2013: 147.8 million	Education	Global: 10%–16% glomerular lesions in 54.8% HCV-positive subjects at autopsy	Treatment of hepatitis C	Impact of treatment on disease burden	Reduce HCC, liver failure, kidney transplant. New medication is very costly	Lower prevalence, unlikely to gain access to expensive therapies	Policies around needle sharing Advocacy against drug abuse Lobby for access to therapy in HIC and LMIC	145–147
Bacterial skin diseases	Global prevalence 2013: 5.8 million	Sanitation, early treatment	Acute PSGN 9 per 100,000 in LMIC Higher frequency or CKD after post-streptococcal GN, worse in adults	Early detection of renal involvement, treatment and follow-up	Contribution to CKD burden in LIC unknown	Likely low	Likely high	Policies to improve child nutrition, school feeding schemes Poverty, overcrowding, scabies prevention and early treatment. Consider screening school children for hematuria, proteinuria	144,145,167
Schistosomiasis	Global prevalence 2013: 290.6 million	Safe water Education	Obstruction (urinary) 2%–62%, chronic glomerulonephritis (hepatosplenic) in 15%	Prompt treatment, screening for obstruction	Obstruction usually not severe, renal function preserved. Regional contribution to ESKD may be 3%–7% (Egypt)	Low	High regional	Public health care policies, neglected tropical diseases Clean water Consider screening school children for hematuria, proteinuria. Prompt access to diagnosis and treatment	132,145,148,168,169
Diarrheal illnesses	Global prevalence 2013: 4.24 million	Safe water, sanitation,	Important cause of AKI worldwide	Appropriate hydration,	Burden of CKD related to diarrhea-associated AKI.	Relatively low, diarrhea-associated HUS	High, important cause of childhood AKI	Public health care policies, sanitation,	145

		nutrition, vaccination		antibiotics when needed	Impact of vaccination on AKI/CKD		through volume depletion, sepsis, HUS	water education, infrastructure, vaccination Advocacy to chlorinate water, handwashing, improve water safety, equitable access to vaccination, education about oral rehydration therapy	
Malaria	Worldwide prevalence 2013: 351 million	Use of ITNs, vector control, prompt treatment with correct drugs	AKI <1% to >50% in adults with severe falciparum malaria. CKD not often reported among survivors	Early screening, diagnosis, and management	Contribution to CKD burden regionally unknown, possible differences among those living in endemic areas or not? May be associated with CKDu	Low	High regional	Public health care policies, vector control, insecticide-treated nets, monitor medication resistance, combat counterfeit medication, introduce RDT Access to prevention, diagnosis, appropriate treatment	136–139,145
Tuberculosis	Worldwide prevalence 2013: 12.1 million	Healthy diet, reduce poverty, reduce HIV	Genitourinary 27% of extrapulmonary TB (obstruction, parenchymal infection, interstitial nephritis)	Prompt diagnosis and full treatment	Low	Low, higher in immigrant, prison, indigenous, immune-suppressed populations	High, regional. Often coinfection with HIV	Public health care policies on detection, supervision of therapy, GeneXpert, management of MDR, XDR, integration with HIV services Poverty, comorbid illness, nutrition, overcrowding, occupational exposure (mining), HIV infection	143,145

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Table 1 | Global relevance of major risk factors for chronic kidney disease and suggested mitigation strategies (Continued)

Risk factor	Global prevalence	Primary prevention	Projected CKD risk	Secondary prevention of CKD	Knowledge gaps	Relevance for HIC	Relevancy for LIC	Advocacy required	Refs
Leptospirosis	Global incidence 1.03 million	Use of ITNs, vector control, prompt treatment	AKI (Weil's disease) 10%–60%	Early diagnosis	Contribution to burden of CKD unknown	Little	High, regional	Public health care policies, neglected tropical diseases Poverty, water quality, overcrowding	137,170
Environmental factors	Unknown risk factor prevalence for CKDu– likely association with environment (heat), occupation, poor fluid intake, coinfections, traditional remedies	Avoid occupational, climate, and environmental hazards	Prevalence 13%–26% in high-risk populations	Hydration Avoid nephrotoxins	Causes and pathophysiology unknown	Low	CKDu major problem in multiple LMIC	Policies around working conditions, environmental contamination	5,139,171
AKI	21% of hospital admissions (global data insufficient for accurate quantification)	Early risk identification, treat underlying cause early, avoid nephrotoxins	Adults: 25.8 per 100 person-yr (CKD), 8.6 per 100 person-yr (ESKD) Children: 3.1 per 100 person-yr (proteinuria), 0.9 per 100 person-yr (ESKD)	Early diagnosis and treatment of AKI	Actual risk of CKD after AKI in population, impact of interventions to reduce AKI on the prevalence CKD	Predominantly hospital acquired, older adults, multiple comorbidities	Predominantly community acquired, adults younger, few comorbidities	Increase awareness of risk of AKI and need for prompt treatment, require accessible methods to diagnose AKI, awareness of CCKD risk requiring long-term follow-up after severe AKI	150,153,154

ACEI, angiotensin converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; ART, antiretroviral therapy; BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; CKDu, chronic kidney disease of uncertain etiology; CVD, cardiovascular disease; DM, diabetes mellitus; ESKD, end-stage kidney disease; GDM, gestational diabetes mellitus; GFR, glomerular filtration rate; GN, glomerulonephritis; HAART, highly active antiretroviral therapy; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIC, high-income country; HT, hypertension; HUS, Hemolytic-uremic syndrome; HZ, hazard ratio; ITN, insecticide-treated nets; LBW, low birth weight; LIC, low-income country; LMIC, low- and middle-income countries; MDR, multi-drug resistance; NSAID, nonsteroidal antiinflammatory drug; OTC, over-the-counter; PEP, postexposure prophylaxis; PPI, proton pump inhibitor; PSGN, post-streptococcal glomerulonephritis; RDT, rapid diagnostic testing; RR, relative risk among those who experineced preeclampsia versus those who did not for the listed outcomes; Rx, treatment; SDG, sustainable development goal; SGA, small for gestational age; TB, tuberculosis; UHC, universal health care; UMIC, upper middle–income country; XDR, extensive drug resistance.

lifestyle factors with the risk of developing CKD.[29–36] Conversely, interventions to manage hypertension and promote weight loss are associated with reduced risks of developing CKD and better outcomes among those living with CKD.[2,37–43]

Gaps. Epidemiological assessment, followed by prioritization of CKD risk factors according to their contribution to the local burden of the disease, is important to determine where public health care efforts should be focused on reducing the population burden of CKD. In addition, existing barriers to the implementation of locally relevant strategies for the prevention and management of diabetes, hypertension, and obesity must be identified. Barriers may include resistance to change in the communities themselves or push back from industry and others that are potentially affected by lifestyle modification campaigns.

Action strategies. Population-based studies are needed to determine the impact of diabetes, hypertension, and obesity prevention programs on the prevalence and incidence of CKD. Longitudinal studies are necessary to understand the impact of prevention programs on the rates of CKD and end-stage kidney disease (ESKD) and related comorbidities, including cardiovascular complications and infections. Studies are required to better understand appropriate risk-benefit thresholds (target hemoglobin A1c, BP, and weight) for CKD prevention and management and to understand interactions between race-ethnicity, genetics, socioeconomic status, and geography as modifiers of CKD risk and progression. The impact of tobacco consumption on CKD needs to be studied further.

Strategies to reduce CKD risk attributable to diabetes, hypertension, and obesity will be most effectively implemented as part of a broad approach to NCD prevention. Interventions to reduce lifestyle-related NCD risk factors are most successful when implemented at both patient and community levels, supported by legislation and regulation.[44] Public health care approaches with the greatest evidence of effectiveness in reducing NCD risk include economic incentives to lower the price of healthy food, taxation on unhealthy food, education and physical activity programs in schools, food advertising restrictions and standards, providing more recreation spaces and facilities, sustained media campaigns for smoking cessation, cigarette packet warnings, restrictions on tobacco advertising, higher taxes on tobacco, and restrictions on smoking in public areas and workplaces.[45] Several countries have made efforts to reduce population consumption of sugary beverages, high-fat foods, and salt with the endorsement of the Panamerican Health Organization and WHO; however, more research is needed to understand which lifestyle interventions will have the greatest impact on CKD burden.[22,46,47]

An example of the importance of rigorous epidemiologic evidence required to inform policymaking and action is the ongoing debate on the utility of sodium reduction as a population measure to reduce BP and CVD.[48–53] Recent studies have demonstrated a J- or U-shaped relationship of sodium intake with BP and mortality.[54–56] The benefit of salt reduction is greater among hypertensive people, but definitive effects on kidney disease outcomes remain uncertain. Interventional studies have demonstrated that estimated glomerular filtration rate (eGFR) and albuminuria (proteinuria) increased with higher salt intake, and a recent study showed that reduction of sodium intake reduced albuminuria.[57] In the United Kingdom, voluntary food-manufacturing targets achieved a lower sodium intake of 15% between 2001 and 2011, which was associated with a decrease in mean BP (3 mm Hg) and 40% reduction in deaths owing to stroke and ischemic heart disease.[50,58] However, the respective role of sodium reduction versus other treatments for hypertension, dyslipidemia, and CVD are not clearly delineated.[50,58]

Implementing population-level approaches to reduce NCDs requires action across multiple sectors of the government and society, as well as a commitment of the governments. This is consistent with the Health in All policy strategies outlined by WHO, which emphasizes the importance of multi-sectoral engagement for the successful implementation of public health care policies.[44,46] At the level of health care departments, health care providers must have the necessary technology, tools, medicines, and services that are required for efficient assessment and control of risk factors. Community engagement and education are crucial to optimize success. Patients themselves are also a key to NCD prevention. In the chronic care model, patient self-care takes on great importance, while the roles and responsibilities of physicians, nurses, and community health care workers are being redefined through innovative strategies and technologies.[21] Ongoing monitoring and evaluation of policy implementation will permit a better understanding of barriers to and facilitators of CKD prevention. This is especially true of LMICs, where the major barriers are quality, price, and availability of drug treatments for diabetes and hypertension. Understanding how such barriers and facilitators vary by jurisdiction, health care system, race-ethnicity, age, sex, and socioeconomic status helps to inform the development of effective local strategies.

Systematic surveillance is recommended for the screening of diabetes, hypertension, and obesity using, for example, the STEPwise approach to surveillance survey model. Once individuals with these conditions are identified, they should be recognized as being at high risk for CKD and should be evaluated for eGFR and albuminuria. Clinical guidelines on BP, blood glucose, and weight and physical activity targets should be clear and easy to implement to optimize CKD risk factor management. Screening and early intervention when CKD is detected were shown to reduce ESKD and be cost-effective.[40,59–61]

Nephrotoxins as risk factors for AKI and CKD

Nephrotoxic agents can cause both AKI and CKD.[62] Nephrotoxin exposure is common in hospitalized patients and may account for up to 25% of AKI cases.[63–65] Common agents associated with AKI include nonsteroidal antiinflammatory

drugs, antibiotics, iodinated contrast media, and chemotherapeutic drugs.[66,67] Clinician and patient education are important to reduce the risk of nephrotoxicity. Where electronic medical records exist, alerts to reduce the risk of nephrotoxic exposure and drug interactions can be activated.[68,69] Electronic medical records can simultaneously be used to monitor prescription practices, responsiveness to alerts and prompts, rates of AKI, and barriers to effective implementation.[70,71] In high-income countries, AKI typically develops during hospitalization and may impact long-term health. For example, CKD (urinary abnormalities, low eGFR, or hypertension) was found in 70% of children 6 months after nephrotoxin-induced AKI.[72]

The list of medications that can induce CKD is steadily expanding. The mechanisms range from interstitial inflammation to glomerular and tubular injury.[73–75] Strategies should be implemented to reduce nephrotoxin-induced AKI and CKD, as well as to emphasize the risks of medication overuse and dose adjustments for eGFR. Detection of medications that lead to CKD is challenging given the long lag time. As recently described for proton pump inhibitors, linkage between clinical and prescription databases can identify novel associations between CKD and medications, which enables ongoing surveillance.[73]

The use of culturally traditional and alternative remedies is common worldwide, reaching over 80% of the population in many regions.[76] The rates of associated AKI and CKD are unknown, although up to 30% of AKI in sub-Saharan Africa may be related to traditional remedy use.[77] In Europe and North America, the market for alternative remedies generates billions of dollars per year.[78] Remedy production is often unregulated, leading to high interproduct variability and underappreciated risk of kidney injury.[79] In LMICs, traditional remedies are often the only affordable means of health care. Given the large number of people worldwide using these remedies, toxicity cannot be universal but instead may relate to individual susceptibility, which remains underinvestigated.[76]

Gaps. The true risk of nephrotoxicity of commonly used medications or remedies is uncertain given the unknown denominators of use. Some medications are known to be nephrotoxic, especially in particular circumstances such as nonsteroidal antiinflammatory drugs with volume depletion. The magnitude of risk, which compounds are most toxic and under which circumstances, and how to best use these compounds safely if no alternatives exist remain unknown. In LMICs, traditional medicines are used for many reasons other than medical ones; therefore, a better understanding of the role that remedies play in people's lives is required.[80] Further studies are required to identify potentially toxic remedies, risk factors that may exacerbate nephrotoxicity, herb-medication interactions, and potentially beneficial compounds.[81–87]

Action strategies. In settings with electronic medical records, the use of medicines and alternative remedies should be captured. These databases will permit the monitoring of prescription practices to establish a true denominator of subjects who are at risk and to permit surveillance for determining associations with nephrotoxicity and potential exacerbating factors. Screening protocols should be developed to identify nephrotoxic effects of medications to improve consistency in case/compound identification and comparability of outcomes. When nephrotoxicity is suspected, attempts should be made to analyze culprit remedies, and detailed case reports should be published. Education of health care practitioners is important to foster regular prescription reviews. Guidelines should emphasize the measurement of eGFR prior to the prescription of potentially nephrotoxic medications, with electronic warnings for medication interactions and risks. Shared pharmaceutical prescription databases will avoid repeat prescriptions or drug interaction potential. Research should continue to develop effective alternative agents with reduced nephrotoxicity.

To reduce the use of nephrotoxic remedies, it is important to ensure that individuals have access to essential medical care and medication. Where alternative remedy use is widespread, strategies should be identified to minimize exposure to nephrotoxins. Such approaches should be customized based on the region, economic realities, and community perspectives to improve safety without alienating groups or challenging fundamental beliefs. Engagement with traditional healers is crucial to foster collaboration, educate on kidney disease, and learn about potentially beneficial remedies. The public and health care workers (HCWs) must be educated about nephrotoxicity and drug interactions relevant to herbal remedies and over-the-counter preparations.[87] Clinicians should be encouraged to ask about alternative remedy use. A global free web–based adverse event reporting site (across income settings) should be developed to gather data and study associations of remedy use with rates of CKD.

Given easy access to alternative remedies, governments should develop policies about the accuracy of advertising and health claims touted on the Internet and require efficacy data similar to that required for pharmaceuticals. Policies should enforce minimum standards of safety, manufacturing, labeling, and adverse event reporting on the alternative remedy industry.

Kidney stones and CKD risk

Kidney stone disease is now recognized as a chronic health condition that is associated with CKD and ESKD risks.[88–92] The association between kidney stones and CKD is partly explained by shared risk factors such as diabetes,[93–95] obesity,[96,97] hypertension,[94,97,98] metabolic syndrome,[99,100] and CVD.[101–103] However, kidney stones may also directly contribute to the development and progression of CKD via urinary tract obstruction and/or infection, nephrocalcinosis, and oxalate nephropathy.[88,104,105] The worldwide prevalence of kidney stones among adults is 5% to 9% and is apparently increasing, with variations between regions and countries.[106,107] The rising global rate of kidney stones may be contributing to the overall CKD burden related to dietary factors, obesity, global warming, and environmental and occupational exposures (e.g., high ambient temperatures,

contact with zinc or cadmium).[90,97,105,107] Individuals who have experienced a single stone event are at an increased risk for a symptomatic stone recurrence (up to 50% within the first 5 years).[105] Therefore, prevention among these individuals is an important strategy to reduce further stone formation and CKD risks.[90] Higher fluid intake, avoidance of low dietary calcium and sweetened beverages and the reduction of dietary sodium and red meat intake reduce stone formation risk.[108–110]

Gaps. A better understanding of regional risk for kidney stones is important to prioritize stone prevention and reduce CKD risk. The regional impact of climate change on kidney stones is unknown. Long-term surveillance should permit a better understanding of the impact of stone prevention strategies (lifestyle habits and medication) and treatments (e.g., lithotripsy and surgery) on the risks of new-onset and progressive CKD. Health care costs for kidney stone disease require further studies. The effectiveness and cost-effectiveness of prevention strategies across populations are unknown.

Action strategies. Tracking mechanisms and research should be developed to determine the relationships between kidney stones and the incidence, prevalence, progression, and complications of CKD in regional contexts. Environmental or occupational hotspots should be detected through surveillance. Understanding stone types and risk factors (e.g., genetics, infections, and diet) are important to inform local prevention strategies. Together with public health care strategies to reduce diabetes, hypertension, and obesity, surveillance activities should include impact on the rates of kidney stones and those of stone-related CKD to identify high-risk groups for targeted prevention and cost-effectiveness.[90] In areas with a high risk for stone formation, public and HCW education campaigns should increase awareness and emphasize simple prevention strategies (e.g., fluid intake and dietary modification). Where occupational exposure is detected as important, engagement with policy makers and employers is important to modify work conditions.[111]

Maternal, fetal, and childhood health as CKD risk factors

Low birth weight (LBW), small for gestational age, and preterm birth (PTB) impact the number of nephrons an individual starts life with and are increasingly being recognized as CKD risk factors.[112,113] In 2010, over 43 million babies in 139 LMICs were born too soon or too small, suggesting many children are born with a CKD risk.[114] Developmental programming for CKD results from many structural, environmental, social, and physical factors that impact maternal and fetal health throughout pregnancy, as well as the child's nutrition and growth.[112] Recent evidence also indicates high birth weight (especially an infant of a diabetic mother), in addition to LBW and PTB, to be a risk factor for obesity, hypertension, diabetes, and CKD.[115–119] Early onset of diabetes in offspring exposed to diabetes *in utero* in part explains the higher CKD risk in these individuals.[115,120] Childhood obesity is also an important risk amplifier for CKD after LBW, small for gestational age, or PTB.[121] Preterm babies are at an increased risk for AKI related to reduced nephron number, frequent nephrotoxin exposure, and comorbidities, which increase their subsequent CKD risk.[122,123] Not only the children of troubled pregnancies are at long-term risk of CKD, however. Women who develop pre-eclampsia/eclampsia have a higher life-time risk of hypertension, CKD, and CVD, and those who experience gestational diabetes mellitus have an increased risk for developing diabetes.[124–126] Preeclampsia occurs in 1% to 5% of pregnancies worldwide, and gestational diabetes mellitus occurs in around 2% to 6% of pregnancies in Europe, but in up to 25% in some LMICs.[125–127] Many individuals at a long-term CKD risk can be identified early in prenatal clinics and delivery rooms.

Gaps. The contribution of maternal and fetal risk factors to the CKD burden is unknown. *In vivo* counting of nephron number is not yet possible and poses an obstacle to further understanding the impact of developmental programming in the kidney. Variability of nephron number between racial and ethnic groups and geographic locations is largely unknown. Tracking fetal size by fundal height, ultrasound, and Doppler velocimetry can detect intrauterine growth restriction, but the impact of interventions during pregnancy or soon after birth on CKD risk is unknown. Similarly, the impact of PTB on CKD requires longitudinal studies. The impact of high birth weight on CKD risk has rarely been studied. Better methods to screen for and treat preeclampsia and its consequences require further studies.

Action strategies. The impact of fetal and early life development on the risk of adult NCDs is underappreciated. Monitoring the incidence of LBW, high birth weight, PTB, and fetal growth restriction is required to understand the burden with regard to the region and to raise awareness of potential long-term risks. Identification of regional and demographic disparities in birth weights or PTB within countries requires specific interventions or intensification of prevention efforts. Babies must be weighed at birth or soon thereafter, and the birth weight and gestational age should be documented in an enduring health record, which is often not done in LMICs.[114,128] Similarly, neonatal AKI should also be documented as a future CKD risk factor and should trigger follow-up. Education of the public, HCW, and traditional birth attendants is required to raise awareness of the long-term risks of LBW, growth restriction, PTB, gestational diabetes mellitus, and preeclampsia for mother and child. Both require early and ongoing education on healthy lifestyles and lifelong follow-up. Engagement with mothers, communities, traditional birth attendants, and HCW is important to encourage optimal feeding of LBW, high birth weight, small for gestational age, and preterm children to ensure healthy growth while avoiding obesity. Ensuring access to essential health care and medications is crucial to optimize child and maternal health.

Given the attention focused on improvements in maternal and child health initiated by the millennium development goals and sustainable development goals, most countries have

some form of data reporting or monitoring.[129] Policies should not focus only on maternal health during pregnancy and at delivery but should also include access to family planning, equity, and education for women, reduction of poverty, and access to better nutrition. Monitoring women throughout pregnancy is important to detect and manage problems early. Innovative programs have improved prenatal clinic visits and deliveries attended by skilled birth attendants.[130] Such programs should be utilized to improve documentation of birth circumstances, maternal preeclampsia, or gestational diabetes mellitus, thereby identifying individuals who require long-term follow-up and to initiate lifestyle education peripartum. In LMICs, engagement with traditional birth attendants is important to build trust and educate them to detect and refer problem cases. Women with preeclampsia should undergo long-term follow-up to determine the impact of interventions to reduce long-term CVD and CKD risks.

Infections as CKD risk factors

CKD and AKI are considered as NCDs, but infections are an important cause of both conditions, especially in LMICs. Infections are also a common cause of AKI worldwide.[64,131,132] The three diseases, namely HIV, malaria, and tuberculosis (TB), that received much attention under the millennium development goals can cause CKD. In 2015, 36.7 million people were living with HIV.[133] The risk of HIV nephropathy (HIVAN) varies from <10% to almost 50% in Africa.[134] HIVAN is a well-recognized form of CKD that can be prevented and treated with access to effective antiretroviral therapy.[134,135] However, the impact of antiretroviral therapy on kidney disease is not straightforward. Although antiretroviral therapy reduces the incidence and rate of HIVAN progression to ESKD, it also reduces the competing risk of death; therefore, the prevalence of HIVAN-ESKD tends to increase in treated populations.[134] Antiretroviral therapy does not reduce the incidence and/or rate of progression of non-HIVAN forms of CKD.[134] Kidney disease prevention in HIV infection is also affected by comorbidities such as diabetes and viral hepatitis and therefore requires additional management and health screening programs.[134,135] In 2015, 241 million cases of malaria were reported worldwide. AKI secondary to malaria occurs in up to 40% of adults with severe infection.[136] Although kidney function typically recovers in survivors, severe AKI may eventually lead to CKD.[136–138] A Sri Lankan study also reported an association of malaria with CKD of unknown cause.[139] Malaria-associated AKI can be prevented by widespread vector control, use of insecticide-treated bed nets, and access to rapid diagnosis and treatment.[136] In 2014, 9.6 million people became infected with TB.[140,141] Genitourinary TB may be a cause of CKD through miliary involvement or urinary obstruction and may occur in 27% of cases with extrapulmonary TB.[142,143] HIV and TB infections frequently coexist; therefore, the combined kidney risk, exacerbated by medication toxicities and interactions, may be higher.

Many infections other than HIV, malaria, and TB increase CKD risk. Impetigo is frequent in adults and children living in disadvantaged conditions. CKD risk among adults with impetigo is high, strongly supporting proactive prevention and early treatment of skin infections as a possible means to reduce CKD risk.[144] The worldwide prevalence of hepatitis B (HBV) was 331 million people in 2013 and that of hepatitis C was 148 million.[145] The global risk of HBV-associated CKD is likely to be under 10%, whereas the risk of hepatitis C-associated CKD is likely to be higher.[146,147] HBV- and hepatitis C-associated CKD may be unrecognized contributors to chronic glomerulonephritis, which is a leading cause of ESKD in LMICs. Other infections such as leptospirosis and schistosomiasis are neglected tropical diseases associated with CKD.[137,148] Given the direct associations among infections, AKI, and CKD, it is likely that strategies to prevent infection will reduce the global CKD burden.

Gaps. The magnitude of regional CKD burden related to specific infections is unknown. How increasing the effectiveness and reach of public health care interventions could reduce the CKD burden needs to be further studied. The impact of the successful treatment of malaria on the incidence of malaria-associated AKI should be tracked, as fewer people may develop endemic immunity and may be more susceptible to severe disease.

Action strategies. Many guidelines mention CKD as a risk factor for infections, but few recognize CKD as a complication. A survey of existing guidelines is necessary to gauge the current level of awareness and intervention for infection as a CKD risk factor. HBV vaccination, for example, successfully reduced the incidence of childhood HBV-associated membranous nephropathy.[149] Efforts should be made to ensure access to vaccinations to reduce infection-associated risks of AKI and CKD. Short- and long-term surveillance for kidney disease in regions where these vaccines are implemented should be conducted to determine the impact. Where the CKD burden associated with a specific infection is high, research is required to develop locally effective and sustainable methods to prevent and treat these infections. Such strategies require partnerships with local policy makers, public health care practitioners, governmental organizations, and communities to raise awareness and develop implementation strategies. HCWs and communities should be educated about the risks of AKI and CKD associated with infections to support prompt diagnosis, institution of i.v. fluids and antibiotics, and avoidance of nonsteroidal antiinflammatory drugs and other nephrotoxins. Governments should suppress the use of counterfeit drugs, which contribute to increasing disease severity and risk of AKI in infections.

AKI as a CKD risk factor

Worldwide, approximately 20% of patients admitted to hospitals develop AKI.[150] This statistic is largely derived from high-income countries where the majority of AKI is hospital acquired. The true AKI incidence in LMICs is less well known

but is likely at least as high.[150,151] Worldwide, it is estimated that 2 million people die of AKI annually.[152] The number of AKI survivors is unknown, and a considerable proportion will develop CKD.[153–155]

Gaps. The actual CKD risk after AKI is not known. Risk modifiers and the long-term impact of AKI prevention on CKD burden are unknown.

Action strategies. Regionally adapted strategies should be promoted to avoid AKI. Given that most AKI cases in high-income countries are hospital acquired, efforts to reduce AKI incidence should focus on increasing awareness among clinicians and encouraging proactive patient management. Strategies may include electronic medical record alerts for AKI risk and medication prescriptions.[68,69,156] In LMICs, the majority of AKI cases are community acquired, suggesting that prevention should start before hospital admission. Strategies include implementation of public health care measures to reduce the risk of infections and use of nephrotoxins; ensure access to clean water; reduce poverty, accidents, and trauma; improve maternal health; and provide access to essential health care and medication. Education campaigns should be conducted in communities and among HCWs to increase awareness of AKI risk, avoid nephrotoxins, and seek health care promptly.[157] Once patients present to a hospital, guidelines and facilities should be available to institute an appropriate therapy. Long-term follow-up of patients with AKI is required to determine the true burden of subsequent CKD and potential risk modifiers.

Conclusions

Morbidity and mortality owing to CKD are increasing worldwide, and CKD is progressively being recognized as an important contributor to the global burden of the disease.[1,8] Major contributors to the CKD burden are the growing frequencies of diabetes, hypertension, and obesity, which are well-established traditional risk factors for CKD. Public health care policies directed to address many lifestyle factors that contribute to these conditions are expected to positively impact CKD risk. Systematic screening for CKD in at-risk individuals is required for timely intervention when needed and to understand the impact of such policies on CKD incidence. The contribution of nontraditional CKD risk factors, including nephrotoxin exposure, kidney stones, fetal and maternal factors, infections, environmental factors, and AKI, to the global CKD burden is unknown. Moreover, many nontraditional risk factors may predominate in LMICs. The impact of reducing nontraditional CKD risk factors requires further studies. Mitigation of nontraditional CKD risk factors will require advocacy efforts to support policy development, implementation of strategies to reduce disparities, improve access to essential health care and maternal and child health, reduce environmental exposures, prevent AKI, better understand traditional remedy use, and prevent infections.[2,3,158] Race-ethnicity, genetics, sex, socioeconomic status, and geography likely modify the impact of CKD risk factors. Effective coordination within health care systems, and importantly in the era of the sustainable development goals, a broad multi-sectoral approach are required to identify and tackle achievable goals to reduce CKD risk factors and thereby the global burden of CKD.

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PAPER 4

THE GLOBAL BURDEN OF KIDNEY DISEASE AND THE SUSTAINABLE DEVELOPMENT GOALS

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The global burden of kidney disease and the sustainable development goals

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Abstract Kidney disease has been described as the most neglected chronic disease. Reliable estimates of the global burden of kidney disease require more population-based studies, but specific risks occur across the socioeconomic spectrum from poverty to affluence, from malnutrition to obesity, in agrarian to post-industrial settings, and along the life course from newborns to older people. A range of communicable and noncommunicable diseases result in renal complications and many people who have kidney disease lack access to care. The causes, consequences and costs of kidney diseases have implications for public health policy in all countries. The risks of kidney disease are also influenced by ethnicity, gender, location and lifestyle. Increasing economic and health disparities, migration, demographic transition, unsafe working conditions and environmental threats, natural disasters and pollution may thwart attempts to reduce the morbidity and mortality from kidney disease. A multisectoral approach is needed to tackle the global burden of kidney disease. The sustainable development goals (SDGs) emphasize the importance of a multisectoral approach to health. We map the actions towards achieving all of the SDGs that have the potential to improve understanding, measurement, prevention and treatment of kidney disease in all age groups. These actions can also foster treatment innovations and reduce the burden of such disease in future generations.

Abstracts in عربي, 中文, Français, Русский and Español at the end of each article.

Introduction

The 17 sustainable development goals (SDGs) were adopted by the United Nations, as successors to the millennium development goals, with the broad goal of achieving healthy people living on a healthy planet.[1] Although only SDG 3, that is, to ensure healthy lives and promote well-being for all at all ages, is specifically focused on health,[1] achievement of all of the SDGs should have health benefits via impacts on the environment, governance and society.

The *Global action plan for the prevention and control of noncommunicable diseases 2013–2020* (hereafter called the 2013 action plan) outlined an approach to reduce the combined mortality from four major categories of noncommunicable disease, i.e. cancer, cardiovascular disease, chronic respiratory disease and diabetes, by 25% by 2025.[2] Previously, these four categories had been prioritized in the 2008–2013 action plan because, collectively, they were believed to account for about 60% of global deaths and it was anticipated that a large proportion of these deaths could be prevented through elimination of shared risk factors, e.g. alcohol and tobacco use, poor diets and inadequate exercise.[3] Although laudable, the 2013 action plan has been criticized for failing to acknowledge the broader drivers of the noncommunicable disease epidemics, other important noncommunicable diseases and the so-called causes of the causes of noncommunicable diseases and failing to place sufficient emphasis on the need for coordinated multisectoral action.[4] We argue that kidney disease represents one of the important noncommunicable diseases missing from the 2013 action plan and that, given the many social and structural factors that directly affect risks and outcomes of kidney disease, multisectoral action to achieve the SDGs will help prevent and control such disease (Table 1).[1]

Global burden

Although often considered a comorbidity of diabetes or hypertension, kidney disease has numerous complex causes.[5] Importantly, such disease has an indirect impact on global morbidity and mortality by increasing the risks associated with at least five other major killers: cardiovascular diseases, diabetes, hypertension, infection with human immunodeficiency virus (HIV) and malaria. For example, the Global Burden of Disease (GBD) 2015 study estimated that 1.2 million deaths, 19 million disability-adjusted life-years (DALYs) and 18 million years of life lost from cardiovascular diseases were directly attributable to reduced glomerular filtration rates.[6,7]

The GBD 2015 study also estimated that, in 2015, 1.2 million people died from kidney failure, an increase of 32% since 2005.[7] In 2010, an estimated 2.3–7.1 million people with end-stage kidney disease died without access to chronic dialysis.[8] Additionally, each year, around 1.7 million people are thought to die from acute kidney injury.[9] Overall, therefore, an estimated 5–10 million people die annually from kidney disease. Given the limited epidemiological data, the common lack of awareness and the frequently poor access to laboratory services, such numbers probably underestimate the true burden posed by kidney disease. It is therefore possible that, each year, at least as many deaths are attributable to kidney disease as to cancer, diabetes or respiratory diseases, three of the four main categories targeted by the 2013 action plan.[2,10,11] In addition, the estimated number of DALYS attributable to kidney disease globally increased from 19 million in 1990 to 33 million in 2013.[12] In 2016, the DALYs associated with chronic kidney disease, along with those associated with cardiovascular disease, cancers, diabetes and neurological disorders, were found to have increased significantly between 1990 and 2015.[6] A report from the GBD 2016 study highlighted the

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Table 1. **The 17 sustainable development goals and their relevance to kidney health, 2015**

Goal	Description	Relevance to kidney health	Relevant SDG 3 targets
1	End poverty in all its forms everywhere	• Improvements in access to nutrition, personal safety and health care should enhance the prevention, detection and management of kidney disease • Should reduce the incidence of catastrophic health expenditure resulting from treatment for kidney disease	3.8
2	End hunger, achieve food security and improved nutrition and promote sustainable agriculture	• Improvements in maternal nutrition and reductions in the frequencies of low birth weight and preterm birth should reduce the risk of CKD • Reductions in the incidence of obesity should cut the risk of CKD, diabetes and hypertension	3.1, 3.2
3	Ensure healthy lives and promote well-being for all at all ages	• Should improve screening for, and the prevention, diagnosis and treatment of, kidney disease • Public health programmes to promote community education, healthy lifestyles and vaccinations could also reduce the risk of AKI and CKD	All
4	Ensure inclusive and equitable quality education for all and promote life-long learning	• Should improve awareness and kidney-health-related knowledge • May reduce use of nephrotoxic remedies and preparations	3.4, 3.5
5	Achieve gender equality and empower women and girls	• Reductions in the numbers of teenage pregnancies and increases in pregnancy spacing may reduce the incidence of the low birth weight, prematurity and pregnancy-related complications that are all risk factors for CKD • There should also be improvements in overall family health	3.1, 3.7
6	Ensure access to water and sanitation for all	• There should be reductions in the incidence of the waterborne diseases and diarrhoeal illnesses that are major causes of AKI and in the incidence of the schistosomiasis that can cause CKD • There should also be reductions in water pollution that can cause CKD	3.9
7	Ensure access to affordable, reliable, sustainable and modern energy for all	• Should broaden opportunities to use mobile health in prevention and treatment and in community and health worker education • Improvements in access to electronic information sharing and data collection could lead to improvements in the epidemiology, monitoring and surveillance of kidney disease	3.9
8	Promote inclusive and sustainable economic growth, employment and decent work for all	• Improvements in personal access to health care, dignity and wealth could lead to improvements in the prevention and early treatment of kidney disease • Improvements in the retention of health-care workers could reduce the so-called brain drain • Task shifting in health care could be facilitated	3.b, 3.c
9	Build resilient infrastructure, promote sustainable industrialization and foster innovation	• Could support innovations to improve the affordability and sustainability of access to diagnosis, facilitate early treatment and secondary prevention and foster cheaper and more efficient means to prevent, diagnose and treat both AKI and CKD • Could also facilitate investigation of the potential benefits of, or risks posed by, traditional remedies for kidney disease	3.b
10	Reduce inequality within and among countries	• Could improve equity in the prevention, diagnosis and care of all forms of kidney disease • Could improve access to expensive therapies, e.g. dialysis, hepatitis C therapy and transplantation • Could improve geographical access to all forms of kidney care	3.1, 3.2, 3.7, 3.8, 3.b, 3.d
11	Make cities inclusive, safe, resilient and sustainable	• Improved warning and protection from disasters could reduce crush-injury-related AKI • Levels of preparedness in mass disasters, including for patients with AKI, CKD or ESKD, should improve • Urban planning to eliminate food deserts and increase physical activity could help reduce diabetes and obesity-related kidney disease • Reductions in exposure to alcohol, drugs and tobacco could also reduce the risk of kidney disease	3.5, 3.6, 3.d
12	Ensure sustainable consumption and production patterns	• Promotion of the environmentally friendly and sustainable local production of dialysis supplies could reduce dialysis costs, create jobs and support the local economy • Any reductions in the need for dialysis should reduce the carbon footprint from dialysis • There may also be adverse effects on kidney health as increasing access to cars and unhealthy processed foods could lead to an increasing prevalence of obesity and access to cigarettes may also increase	3.4, 3.5, 3.9

(*continues. . .*)

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Goal	Description	Relevance to kidney health	Relevant SDG 3 targets
13	Take urgent action to combat climate change and its impacts	• Global warming may have contributed to an epidemic of Central American nephropathy and to CKD of unknown origin that appears related to dehydration and toxin exposure • The adverse effects of climate change on the transmission of pathogens causing infectious disease and poverty may increase the risk of CKD	3.2, 3.3, 3.d
14	Conserve and sustainably use the oceans, seas and marine resources	• Exposure to marine pollution may increase the risk of CKD	3.9, 3.d
15	Sustainably manage forests, combat desertification and halt and reverse land degradation and halt biodiversity loss	• Any reduction in the leaching of toxins from industrial waste into ground water could reduce the risk of the CKD associated with such pollution	3.9, 3.d
16	Promote just, peaceful and inclusive societies	• Any reduction in armed conflict could reduce the risk of AKI associated with crush injuries and major trauma and improve food security • The incidence of low birth weight, which is a risk factor for CKD, tends to increase during wars • Among prisoners and other marginalized populations, improvements in equity and justice could facilitate the prevention, diagnosis and treatment of kidney disease	3.d
17	Revitalize the global partnership for sustainable development	• Improved global partnerships for health-care financing and regulation and health-related development and research could accelerate our understanding of kidney disease, reduce inequities in kidney care and reduce so-called transplant tourism	3.d

AKI: acute kidney injury; CKD: chronic kidney disease; ESKD: end-stage kidney disease; SDG: sustainable development goal.

important omission of focus on chronic kidney disease and suggested that "the SDG agenda offers at best a minimal platform for drawing attention to the health care and monitoring needs of [chronic kidney disease]."[13]

Kidney disease is associated with a tremendous economic burden. High-income countries typically spend more than 2–3% of their annual health-care budget on the treatment of end-stage kidney disease, even though those receiving such treatment represent under 0.03% of the total population.[14] In 2010, 2.62 million people received dialysis worldwide and the need for dialysis was projected to double by 2030.[8] Globally, the total cost of the treatment of the milder forms of chronic kidney disease appears to be much greater than the total cost of treating end-stage kidney disease. In 2015, in the United States of America, for example, Medicare expenditures on chronic and end-stage kidney disease were more than 64 billion and 34 billion United States dollars, respectively.[15] Much of the expenditure, morbidity and mortality previously attributed to diabetes and hypertension are attributable to kidney disease and its complications.[12,16]

Worldwide, important risk factors for kidney disease include diarrhoeal diseases, HIV infection, low birth weight, malaria and preterm birth, all of which are also leading global causes of DALYs.[12] Risks of kidney disease span the life-course and environmental, infection and lifestyle etiologies.[17] If risk factors are identified early, acute kidney injury and chronic kidney disease can be prevented and, if kidney disease is diagnosed early, worsening of kidney function can be slowed or averted by inexpensive interventions, several of which are on the World Health Organization's (WHO's) so-called best buys list for noncommunicable disease management.[18] Such interventions include counselling for cardiovascular disease, diabetes and hypertension, drug therapy, tobacco control, promotion of physical activity and the reduction of salt intake through legislation and food labelling. The timely identification and management of acute kidney injury and chronic kidney disease represent the most effective strategy to address the growing global burden sustainably.[4,5] By advocating for a multisectoral approach, as a means to achieving the SDGs, it should be possible to reduce the incidence of kidney disease globally.[19] We discuss the kidney-health-related opportunities offered by attempts to achieve each SDG (Table 1).

SDGs and kidney health

SDGs 1, 3.8, 3.b and 10

In high-income countries, lower socioeconomic status is associated with greater risk of end-stage kidney disease because of behavioural and metabolic risk factors and reduced access to care.[20] In low- and middle-income countries, the burden posed by such poverty-related kidney disease is even greater, because of associated infections, hazardous work, poor education and poor maternal health. In all countries, poverty is associated with lack of social protection and transportation, poor housing and unemployment.[20] Lack of transportation restricts access to care even when treatment costs are not a major barrier.[20] Poverty and lower socioeconomic status have been specifically identified as independent risks for both incident chronic kidney disease and the more rapid progression of such disease.[20] In low-income countries where treatment costs have to be paid directly by patients, a month's supply of essential medications for the treatment of chronic kidney disease can cost up to 18 days' wages[21] and the corresponding out-of-pocket costs of dialysis, for acute kidney injury or end-stage kidney disease, are much higher.[22,23] In South Africa, where limited access to dialysis is government-funded, patients who are otherwise eligible for dialysis are frequently declined access because of their socioeconomic circumstances.[24] For those who do access dialysis, the financial burden is exacerbated because they cannot be employed while receiving dialysis or travelling to and from the provider.

Promotion of universal health coverage should reduce the financial hardship of patients with kidney disease and improve access to kidney care.[25] The goal of eradicating poverty spans all of the other SDGs and is fundamental to improving kidney health. In turn, achievement of each SDG promises to promote equity and reduce poverty.[20]

SDG 2

Many low-income countries have problems with undernutrition and overnutrition, both are risk factors for kidney disease. Malnutrition predisposes young children to infections, e.g. diarrhoeal diseases and pneumonia, that are important risk factors for acute kidney injury.[22] Among girls and female adolescents, undernutrition leads to underweight mothers and low-birthweight offspring.[26] Low birth weights, preterm births and pregnancies affected by diabetes and pre-eclampsia, which, combined, may represent up to 20% of pregnancies worldwide, are all associated with increased lifetime risk of chronic kidney disease in both mothers and children.[26] Obesity increases the lifetime risk of end-stage kidney disease[17] and maternal obesity is associated with adverse outcomes in pregnancy,[26] including the gestational diabetes and preterm births that are associated with increased risk of chronic kidney disease.

Adequate nutrition is a key tool for reducing the burden of chronic kidney disease. Groups with very low incomes often live in areas where access to healthful foods is very limited or non-existent.[20] Some population-level strategies, e.g. public education about healthful food choices, regulation of the fat, salt and/or sugar contents of food and the regulation of programmes for the provision of public and/or school meals, can all improve kidney health.[27] Reduction in dietary salt is proposed as a cost-saving best buy with great potential to avert deaths from kidney disease. Similarly, a tax on high-sugar beverages, as introduced in Mexico, where chronic kidney disease is the second leading cause of death, can lead to sustained decreases in the purchase of taxed drinks and may reduce diabetes-related kidney disease over time.[28]

SDG 3

SDG 3 has many links to better kidney health (Table 2 available at: http://www.who.int/bulletin/volumes/96/6/17-206441) including optimization of fetal development, prevention of infections, reduction of the mortality and morbidity of cardiovascular disease and mitigation of environmental exposures. The Global Kidney Health Atlas has provided an overview of the main gaps in kidney care globally: an absence of relevant policies, shortages of essential medications, reliable epidemiological data, relevant workforce capacity, infrastructure and research capacity and a persistent reliance on out-of-pocket payments.[29] The Atlas emphasizes the need for a health-system-wide approach to kidney care and provides a baseline against which to measure progress. Work towards reducing the global burden of kidney disease will contribute to achieving SDG 3 (Table 2).

SDGs 4 and 5

Because they are, in general, responsible for most child care and housework, women in low- and middle-income countries may face greater challenges if they have chronic kidney disease – and other noncommunicable diseases, than men with similar health problems.[30] Heavy demands on their time may explain why, even though chronic kidney disease is more common among women than men, fewer women than men receive dialysis.[30] Child marriage and lack of access to family planning contribute to poor maternal health and increased risk of obstetrical complications, including acute kidney injury.[31] Among urban adults in the United States, both gender and race appeared to affect glomerular filtration rates.[32] Achievement of equity for women worldwide should reduce the burden of kidney disease.

SDG 6

Globally, almost 800 million people lack access to safe water and 2.5 billion lack access to optimal sanitation.[33] In low- and middle-income countries, waterborne and pestilent diseases associated with poor hygiene and sanitation are major causes of acute kidney injury and chronic kidney disease.[34] Enteric diarrhoeal deaths, associated with lack of safe water, cause over 1 million deaths annually.[13] Most of these deaths occur in children younger than five years and many can be attributed to dehydration-related acute kidney injury.[13] Non-enteric diseases caused by waterborne pathogens, e.g. leptospirosis and schistosomiasis, are also major causes of kidney disease in low- and middle-income countries.[34]

Local availability of clean water would be expected to reduce the risk of diarrhoea-related acute kidney injury.[35] Beyond infection-related kidney complications from contaminated water and poor sanitation, additional challenges exist. Water containing organic perfluoroalkyl acids and heavy metals has been associated with chronic kidney disease in several settings and pesticide-contaminated well water may contribute to the risk of some chronic kidney disease observed in Sri Lanka.[36] Dehydration, in conjunction with heat stress, may have contributed to the epidemic of chronic kidney disease observed among young, economically productive male labourers in Central America and South-East Asia.[36] The global burden of kidney disease should be reduced by ensuring the availability of clean water and adequate sanitation.

SDGs 7 and 12–15

Climate change, degradation of biodiversity, forest and land, and loss of marine resources, all likely increase the risk of kidney disease through multiple mechanisms, e.g. increases in food insecurity, the incidences of heat-related illness and infectious diseases and pollution.[37] Deforestation and land degradation can bring humans into greater contact with vector-borne and waterborne pathogens, such as enteric bacteria and other pathogens that can directly cause kidney disease, e.g. those causing dengue fever, leishmaniasis, leptospirosis, malaria, schistosomiasis, trypanosomiasis and yellow fever.[38]

Reducing the global burden of kidney disease in turn will also be critical for mitigating some of the environmental impacts of dialysis. Each year, for example, the haemodialysis given to more than 2 million people requires 160 billion litres of water and generates over 900 000 tonnes of, predominantly plastic waste.[39] Clean, local production of dialysis supplies, the reprocessing of dialysis filters, the reuse of dialysis water, solar-powered dialysis and waterless dialysis are all promising strategies that could creduce the environmental footprint of dialysis as well at its costs.[39]

SDGs 8, 10 and 17

Within low- and middle-income countries, access to dialysis is highly inequitable.[8] Despite its relative cost–effective-

ness, access to transplantation is even more inequitable because of cultural, financial and legislative barriers and infrastructural limitations.[40] In the face of extreme social inequalities and a demand for transplants that markedly exceeds the supply, the trafficking of kidneys and other human organs remains a major concern.[40]

Disparities in the burden of kidney disease, which are particularly complex, arise from biological, environmental, genetic, lifestyle and sociocultural factors[20] and need to be addressed via multilevel, systematic interventions.[34] An example of the complexities involved has been described in the United States. There, in general, compared with other patients with similar disease, patients with chronic kidney disease from ethnic and racial minorities have delayed referral for care, lower incomes, report poorer physician–patient relationships and have less access to health care in general.[20] The pervasive disparities in kidney disease will have to be addressed before SDGs 8, 10 and 17 can be achieved.

SDGs 3.6, 3.d, 9 and 11

Rapidly occurring urbanization has contributed to the rise of kidney disease and other noncommunicable diseases in low- and middle-income countries.[41] In addition to the commonly associated lifestyle changes, e.g. a switch to high-calorie, sodium-rich diets and decreased physical activity, rapid urbanization has led to crowded cities with environmental pollution, a limited infrastructure and poor levels of sanitation and waste disposal.[42] Such urbanization also means that more and more people are living in settings where a growing prevalence of noncommunicable diseases, e.g. diabetes, hypertension and obesity, is juxtaposed with environmental toxins and numerous infectious diseases.[42] These changes portend a synergistic growth in the global burden of kidney disease. There may already be evidence of such growth in the ever-higher ranking of chronic kidney disease among leading cause of deaths, across all country income categories, between 1990 and 2016.[13]

By building resilient infrastructure while promoting sustainable industrialization, it should be possible to enhance health-care access while simultaneously reducing the risk of kidney disease. In low- and middle-income countries, urban planning, to improve hygiene and sanitation and reduce population densities and the transmission of the pathogens causing enteric infections, schistosomiasis and tuberculosis, should reduce the incidence of acute kidney injury and chronic kidney disease.[17] At the same time, by promoting the development of parks, paths and efficient transport systems, urban planning could increase general levels of physical activity and so help reduce the risk of obesity-related kidney disease.[42]

The effective prevention of chronic kidney disease will require engagement with the corporate sector, whose interests may be in conflict with those of public health.[43] Novel strategies are required to create incentives for the corporate sector to promote public health.[44] Even under optimal circumstances, kidney disease cannot always be prevented and strategies to reduce the economic, physical and social burdens of end-stage kidney disease are needed. Innovative mechanisms to reduce dialysis costs and make dialysis less dependent on electricity and water could multiply opportunities for access to dialysis, especially in low- and middle-income countries.[39] Innovation is also required to improve access to transplantation. Although opt-out or presumed-consent strategies have been proposed as a way of increasing the supply of organs from deceased donors, they remain contentious.

Acute kidney injury after a road-traffic collision may result from rhabdomyolysis and multi-organ failure as well as blunt or penetrating kidney injury.[45] Natural disasters are associated with increased rates of crush-injury-induced acute kidney injury and frequently lead to life-threatening interruptions of treatment among those with end-stage kidney disease.[46] Similarly, forced migrants with chronic or end-stage kidney disease can face dangerous interruptions in their treatment or receive inadequate care,[47] even in a high-income country such as the United States.[48] Continued action on reducing the burden of road-traffic injuries and supporting efforts to integrate noncommunicable disease management into humanitarian relief efforts should help to reduce the burden of chronic and end-stage kidney disease.[46]

SDG 16

Exposure to armed conflict can result in acute kidney injury caused by crush injury and rhabdomyolysis and the severity of injuries sustained in combat strongly correlates with the subsequent risk of chronic kidney disease.[49] Kidney disease is common in incarcerated populations and, in terms of their kidney health, prisoners may face a triple burden: of excess risk of kidney disease and its risk factors, of barriers to preventive care for established chronic kidney disease and of the suboptimal management of end-stage kidney disease.[50] As an important step towards improving global health, much work is required globally to reduce conflict and disparities and enhance peace.

Policy perspective

The net health burden of kidney disease is substantial, growing and driven by complex interactions, between communicable and noncommunicable diseases, that are shaped by upstream environmental and socioeconomic disparities. Although kidney disease, whether acute, chronic or end-stage, can be extremely costly, it is also potentially preventable and adverse outcomes can often be delayed or prevented by inexpensive interventions. Kidney disease is highly prevalent, spans the life course and has substantial financial implications. Our response to such disease requires a systematic policy approach, to strengthen all relevant aspects of the health system and to facilitate integration of the promotion of kidney health within a comprehensive horizontal programme for the prevention and treatment of noncommunicable diseases (Table 2).

Within each country, the local burden and prevalence of kidney disease and its risk factors and the local capacity to identify and manage such disease must be determined, as a prerequisite for fair priority setting and appropriate policy development. Diagnosis of kidney disease is often hampered by a lack of awareness among health-care workers and at-risk communities and by inadequate and often erratic access to laboratory testing. Broad policies are increasingly being adopted globally to curb dietary intakes of fat, salt and sugar. Such policies all promise to reduce the burden of chronic kidney disease. The burden of acute kidney injury could be reduced through the ongoing commitment to reduce the transmission of the pathogens causing infectious diseases.

We need universal health coverage to tackle kidney disease successfully

and ensure effective screening, prevention and early treatment. Effective and transparent policies to govern access to care for end-stage kidney disease should only be developed after there has been a thorough attempt to determine the local health priorities, especially in resource-poor settings. Engagement with all relevant stakeholders and innovative financing strategies will be required to maximize equitable access to care. The bidirectional and synergistic interplay between kidney disease and all of the SGDs must be acknowledged in the development of a multisectoral approach. Policies that foster domestic and international collaboration, improve occupational and road safety, limit organ trafficking, promote access to education and gender equality, reduce unemployment and tackle the predicted adverse effects of climate change may all reduce kidney disease and/or the disparities in the care for such disease. However, as noted by the United Nations Secretary-General in December 2017, in the control and prevention of noncommunicable diseases, "political commitments have not often been translated into concrete action."[51] On its own, policy-making is insufficient. Monitoring the impact of policies on kidney disease and the risk factors for such disease needs to be integrated into existing surveillance activities. Health workers and communities must be empowered to advocate for, and hold policy-makers accountable for, kidney health, as an important step towards achievement of the SDGs. ■

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ملخص

العبء العالمي لمرض الكلى وأهداف التنمية المستدامة

وُصف مرض الكلى بأنه المرض المزمن الأكثر عرضة للإهمال. ولا سبيل إلى الخروج بتقديرات موثوقة لحجم العبء العالمي لمرض الكلى من دون إجراء المزيد من الدراسات المستندة إلى الشرائح السكانية، إلا أن هناك مخاطر محددة تقع في مختلف أنحاء الطيف الاجتماعي الاقتصادي، ما بين الفقر إلى الثراء، ومن سوء التغذية إلى السِمنة الزائدة، وفي البيئات الزراعية إلى ما بعد الصناعية، وعلى مَدار الحياة بدءًا من المولودين حديثًا حتى المسنين. وهناك عدد من الأمراض السارية وغير السارية التي تؤدي إلى إصابة الكلى بمضاعفات، ولا يتسنى للعديد من المصابين بمرض الكلى سبل الحصول على الرعاية. كما أن لمسببات أمراض الكلى وتبعاتها ونفقاتها تبعات تقع على عاتق سياسة الصحة العمومية في جميع البلدان. كما تتأثر مخاطر الإصابة بمرض الكلى بعوامل الأصل العرقي والنوع الاجتماعي والموقع ونمط الحياة. وقد يؤدي تزايد الفوارق الاقتصادية والصحية، وعوامل الهجرة، والانتقال الديموغرافي، وظروف العمل غير الآمنة، والتهديدات البيئية، والكوارث الطبيعية، والتلوث إلى تقويض المحاولات الساعية إلى الحد من نسب الإصابة والوفيات الناتجة عن مرض الكلى. ويلزم اتباع نهج متعدد القطاعات للتعامل مع العبء العالمي لمرض الكلى. وتؤكد أهداف التنمية المستدامة على أهمية اتباع نهج متعدد القطاعات للتعاطي مع الصحة. ونحن نعمل على توجيه الإجراءات نحو تحقيق جميع أهداف التنمية المستدامة القادرة على تحسين مستويات فهم مرض الكلى وقياسه والوقاية منه وعلاجه في جميع الفئات العمرية. كما يمكن لهذه الإجراءات أن تعزز من سبل التطوير في مجال العلاج، وتحد من حجم العبء الناتج عن المرض في أوساط الأجيال المقبلة.

摘要

全球肾病负担和可持续发展目标

肾病被视为全球最被忽视的慢性疾病。全球肾病负担的可靠预估需要更多基于人群的研究，但是特定风险的发生横跨社会各经济范围，从贫困到富裕，从营养不良到肥胖，从农耕时代到后工业时代，生命周期从新生儿到老年人。肾脏并发症导致一系列可传染和不可传染的疾病，许多患有肾病的人缺乏治疗途径。肾病的成因、结果和成本对所有国家的公众健康政策都有影响。肾病的风险也受种族、性别、地点和生活方式的影响。日益扩大的经济健康差距、移民、人口转型、不安全的工作条件和环境威胁、自然灾害与污染可能会阻碍试图降低肾病发病率和死亡率的努力。解决全球肾病负担需要多部门合作。可持续发展目标强调多部门合作解决健康问题的重要性。我们列出达成可持续发展目标所采取的措施，这些措施有提升各年龄群体对肾病理解、测量、预防和治愈的潜力。这些措施也可以促进治疗创新，减轻子孙后代的肾病负担。

Résumé

Charge mondiale de la maladie rénale et objectifs de développement durable

La maladie rénale est décrite comme la maladie chronique la plus négligée. Si d'autres études en population sont nécessaires pour établir des estimations fiables de la charge mondiale de la maladie rénale, les risques spécifiques sont présents dans l'ensemble du spectre socioéconomique, à la fois en situation de pauvreté et de richesse, de malnutrition et d'obésité, dans des environnements agricoles et postindustriels, et à tous les âges, aussi bien chez les nouveau-nés que chez les personnes âgées. Diverses maladies transmissibles et non transmissibles entraînent des complications rénales et de nombreuses personnes atteintes de maladie rénale n'ont pas accès aux soins. Les causes, les conséquences et les coûts de la maladie rénale ont une incidence sur la politique de santé publique dans tous les pays. Le risque de développer une maladie rénale est également influencé par l'origine ethnique, le sexe, le lieu et le mode de vie. L'accroissement des disparités économiques et sanitaires, les migrations, la transition démographique, les conditions de travail dangereuses, les menaces environnementales, les catastrophes naturelles et la pollution sont susceptibles de faire échouer les tentatives de réduction de la morbidité et de la mortalité

liées à la maladie rénale. Une approche multisectorielle est nécessaire pour faire face à la charge mondiale de la maladie rénale. Les objectifs de développement durable (ODD) soulignent l'importance d'une approche multisectorielle en matière de santé. Nous établissons une cartographie des actions à entreprendre pour atteindre tous les ODD qui sont susceptibles d'améliorer la connaissance, la mesure, la prévention et le traitement de la maladie rénale dans toutes les tranches d'âge. Ces actions peuvent également favoriser les innovations thérapeutiques et réduire la charge de cette affection pour les générations futures.

Резюме

Глобальное бремя хронической болезни почек и цели в области устойчивого развития

Хроническая болезнь почек известна как одно из тех хронических заболеваний, которым уделяется меньше всего внимания. Надежные оценки глобального бремени хронической болезни почек требуют проведения исследований, более ориентированных на популяционный уровень, но определенные риски возникают во всем социально-экономическом спектре: от нищеты до богатства, от недоедания до ожирения, от аграрного до постиндустриального сегментов общества, а также в течение всей жизни от новорожденных до взрослых людей. Ряд инфекционных и неинфекционных заболеваний приводит к осложнениям, затрагивающим почки, а многие люди с хронической болезнью почек не имеют возможности получить медицинскую помощь. Причины, последствия и расходы, связанные с заболеваниями почек, имеют значение для политики общественного здравоохранения во всех странах. Риск развития хронической болезни почек также зависит от этнической принадлежности, пола, территории проживания и образа жизни. Рост диспропорций в области экономики и здравоохранения, миграция населения, демографические изменения, небезопасные условия труда и экологические угрозы, стихийные бедствия и природное загрязнение могут помешать попыткам снизить заболеваемость хронической болезнью почек и связанную с ней смертность. Для решения проблемы глобального бремени хронической болезни почек необходим многосекторальный подход. Цели в области устойчивого развития подчеркивают важность многосекторального подхода к здравоохранению. Авторы составили план действий по достижению всех целей в области устойчивого развития, которые могут улучшить понимание аспектов хронической болезни почек во всех возрастных группах, а также исследование, профилактику и лечение этой болезни. Эти действия могут также способствовать инновациям в области лечения и уменьшить бремя этого заболевания для будущих поколений.

Resumen

La carga global de la insuficiencia renal y los objetivos de desarrollo sostenible

La insuficiencia renal se ha descrito como la enfermedad crónica más olvidada. Serían necesarios más estudios basados en la población para obtener estimaciones fiables de la carga mundial de la insuficiencia renal, pero existen riesgos específicos en todo el espectro socioeconómico desde la pobreza hasta la prosperidad, desde la desnutrición hasta la obesidad, en contextos agrarios y postindustriales, y a lo largo de la vida desde recién nacidos hasta la tercera edad. Una variedad de enfermedades contagiosas y no contagiosas producen complicaciones renales y muchas personas que padecen una insuficiencia renal no tienen acceso a la atención. Las causas, las consecuencias y los costes de las insuficiencias renales tienen implicaciones para la política de salud pública en todos los países. Los riesgos de la insuficiencia renal también están influenciados por la raza, el sexo, la ubicación y el estilo de vida. El aumento de las disparidades económicas y de salud, la migración, la transición demográfica, las condiciones de trabajo inseguras y las amenazas ambientales, los desastres naturales y la contaminación pueden frustrar los intentos de reducir la morbilidad y la mortalidad por insuficiencia renal. Se necesita un enfoque multisectorial para abordar la carga mundial de la insuficiencia renal. Los Objetivos de Desarrollo Sostenible (ODS) hacen hincapié en la importancia de un enfoque multisectorial de la salud. Planificamos las acciones para alcanzar todos los ODS con el potencial de mejorar la comprensión, la medición, la prevención y el tratamiento de la insuficiencia renal en todos los grupos de edad. Estas acciones también pueden fomentar innovaciones en el tratamiento y reducir la carga de dicha enfermedad en las generaciones futuras.

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Table 2. **Relevance of the targets of sustainable development goal 3 to kidney disease, 2015**

Target	Description	Relevant kidney condition	Strategies or actions to reduce risk of kidney disease	Policies facilitating improved kidney health
3.1	By 2030, reduce global maternal mortality to less than 70 deaths per 100 000 live births	Pregnancy-related AKI and pre-eclampsia	• Improve access to antenatal care and institutional deliveries and the recognition of pregnancy complications, e.g. eclampsia, pre-eclampsia and peripartum haemorrhage • Identify, during antenatal care or at delivery, mothers at risk, for education and follow-up to reduce long-term risk of maternal CKD and cardiovascular disease associated with pre-eclampsia	UHC Promotion of gender equity Public health promotion of healthy lifestyles through education and regulation of unhealthy food and tobacco consumption Promotion of the consumption of healthy food
3.2	By 2030, end preventable deaths of neonates and children under 5 years of age, with all countries aiming to reduce neonatal mortality to no more than 12 deaths per 1000 live births and mortality among children under 5 years of age to no more than 25 deaths per 1000 live births	Perinatal AKI	• Reduce prematurity • Avoid or reduce perinatal use of nephrotoxins, e.g. aminoglycoside antibiotics and non-steroidal anti-inflammatory drugs • Optimize neonatal nutrition	UHC Education of health-care workers Enhancement of the capacity and infrastructure for detection and surveillance
		CKD and hypertension in later life	• Reduce prematurity and low birth weight, which are both risk factors for low nephron numbers	UHC to improve access to prevention and screening services Public health promotion of healthy lifestyles through education and regulation of unhealthy food and tobacco consumption Adoption and implementation of the FCTC
		Diarrhoea-associated and HUS-associated AKI, post-infectious glomerulonephritis	• Improve sanitation and access to vaccinations and medical care	Development of public health policy to improve disease surveillance and response to outbreaks
3.3	By 2030, end the epidemics of AIDS, malaria, neglected tropical diseases and tuberculosis, and combat hepatitis, waterborne diseases and other communicable diseases	HIV nephropathy	• Provide equitable access to services for the prevention and treatment of HIV infection	UHC Enactment of protections for women victims of domestic violence and sexual assault Taking action, including legal, policy and regulatory reforms, to ensure full political enfranchisement for women Legislation for the protection of sex workers
		Malaria-associated AKI, black water fever	• Prevent and provide early treatment of malaria and combat both availability of fake medication and emergence of resistance to antimalarials	Development of public health policy to improve disease surveillance and response to outbreaks Reforming of pharmaceutical supply chains and enhancement of regulations to combat fake medicines
		CKD – a risk factor for tuberculosis	• Increase awareness of risk • Adapt medication doses according to kidney dysfunction	Development of public health policy to improve disease surveillance and the effectiveness of diagnosis and treatment Development of innovative interventions to improve labour conditions and conditions in prisons
		Hepatitis-associated glomerulonephritis and hepatorenal syndrome	• Improve access to vaccination and treatment for hepatitis B and C • Reduce hepatitis-associated inflammation and immune-complex deposition • Reduce kidney-disease-associated cirrhosis and liver failure	Provision of public education and UHC Development of care models integrating traditional healers. Legislation on alcohol consumption to reduce high-risk drinking
		CKD from infections	• Prevent and treat Hantavirus, leptospirosis and scrub typhus	Development of public health policy to improve disease surveillance and the effectiveness of diagnosis and treatment
		Urinary obstruction	• Reduce schistosomiasis • Diagnose and treat kidney tuberculosis adequately, to reduce long-term obstruction of urinary tract	Development of public health policy to improve disease surveillance and response to outbreaks

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Target	Description	Relevant kidney condition	Strategies or actions to reduce risk of kidney disease	Policies facilitating improved kidney health
3.4	By 2030, reduce by one third premature mortality from noncommunicable diseases through prevention and treatment and promote mental health and well-being	CKD	• Prevent and screen for CKD, improve access to early diagnosis and effective treatment for CKD, provide equitable access to treatment for kidney failure, i.e. dialysis and transplantation, and strengthen access to options for lifestyle improvement • Reduction in CKD could reduce morbidity and mortality associated with some other diseases, e.g. cancer, diabetes and liver disease	UHC Enactment of protections for women victims of domestic violence and sexual assault Taking action, including legal, policy and regulatory reforms, to ensure full political enfranchisement for women Promotion of healthy lifestyles through education and regulation of unhealthy food consumption Adoption and implementation of FCTC Enhancement of capacity and infrastructure for detection and surveillance Development of care models integrating traditional healers. Enhancement of occupational safety standards Development of transparent policies governing access to expensive therapies such as dialysis and transplantation
		Cardiovascular disease	• Reduce CKD, this should reduce the burdens posed by global hypertension and cardiovascular disease and the associated mortality	
		AKI	• Prevent AKI through improved access to sanitation and vaccination, decrease reliance on toxic traditional remedies, improve access to early diagnosis and effective treatment for AKI and provide equitable access to dialysis • Reduction in AKI could reduce morbidity and mortality associated with some other conditions, e.g. heart failure, liver disease, sepsis and surgery	
3.5	Strengthen the prevention and treatment of substance abuse, including narcotic drug abuse and harmful use of alcohol	CKD and hypertension in later life	• Reduce low birth weight associated with alcohol use, smoking and substance abuse in pregnancy • Alcohol use and smoking are risk factors for CKD progression	UHC Enactment of protection for women victims of domestic violence and sexual assault Taking action, including legal, policy and regulatory policy reforms, to ensure full political enfranchisement for women Promotion of urban safety Legislation and regulation of alcohol consumption Adoption and implementation of FCTC Legislation for the protection of sex workers
		HIV and hepatitis-associated kidney disease, infectious glomerulonephritis	• Reduce infections transmitted by intravenous drug use	
		Rhabdomyolysis	• Prevent rhabdomyolysis by increasing awareness and providing treatment for drug withdrawal and delirium tremens	
3.6	By 2020, halve the number of global deaths and injuries from road traffic accidents	AKI	• Prevent trauma-related crush injury or blunt kidney trauma	Enforcement of existing traffic laws and reform of traffic laws to reduce road trauma Promotion of occupational safety Development and building of infrastructure and safe roads, with capacity to absorb urban growth
		CKD	• Prevent accident-related losses in employment, increases in poverty and reductions in access to health care	
3.7	By 2030, ensure universal access to sexual and reproductive health-care services, including for family planning, information and education, and the integration of reproductive health into national strategies and programmes	Pregnancy-related AKI, CKD	• Empower women, increase spacing of pregnancies and reduce teenage pregnancies • Reduce risk of low birth weight and preterm birth, as these can adversely affect kidney health of the child	Promotion of access to education for all and family planning, gender equity and UHC Strengthen legislation on access to safe abortion and the protection of sex workers
3.8	Achieve UHC, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all	AKI, CKD	• Provide universal access to basic health care and services for the diagnosis, prevention and treatment of all kidney disease and its risk factors, e.g. diabetes and hypertension	Promotion of innovative financing, regulation of the pricing of medical products and UHC Monitoring of catastrophic health expenditure

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Target	Description	Relevant kidney condition	Strategies or actions to reduce risk of kidney disease	Policies facilitating improved kidney health
3.9	By 2030, substantially reduce the number of deaths and illnesses from hazardous chemicals and air, water and soil pollution and contamination	CKD of unknown origin, observed in Egypt, India and Sri Lanka, and Balkan nephropathy	• Reduce exposure to environmental toxins that may be associated with CKD, e.g. aristolochic acid and cadmium and others	Promotion of environmental protection and safety Promotion of sustainable agriculture and fishing Commitment to combat climate change
3.a	Strengthen the implementation of WHO's FCTC in all countries, as appropriate	CKD	• Reduce tobacco smoking, a risk factor for cardiovascular disease and mortality, haematuria, low birth weight and proteinuria	Adoption and implementation of FCTC
3.b	Support the research and development of vaccines and medicines for the communicable and noncommunicable diseases that primarily affect developing countries, provide access to affordable essential medicines and vaccines, in accordance with the Doha Declaration on the TRIPS Agreement and Public Health, which affirms the right of developing countries to use to the full, the provisions in the TRIPS Agreement regarding flexibilities to protect public health and, in particular, provide access to medicines for all	AKI	• Provide and support the uptake of vaccines that can prevent diarrhoeal illness, sepsis and other infections that can cause AKI and can prevent low birth weight in pregnancy • Support prompt access to the intravenous fluid and appropriate antibiotics that can prevent AKI and glomerulonephritis[d] • Vaccination in pregnancy can reduce the risk of low birth weight • Vaccination during pregnancy can reduce the incidence of low birth weight	Promotion of budget allocation for locally relevant research Strengthening and empowerment of local research ethics committees Utilization of TRIPS Agreement exemptions Enhancement of the regulation of generic medication Monitoring of medication supply and use Promotion of health technology assessments Development of transparent policies governing access to expensive therapies, e.g. dialysis and transplantation Development of innovative financing models to reduce costs of dialysis and transplantation Implementation and enforcement of the Istanbul Declaration against organ trafficking Development of legislation regarding brain death and organ donation Opt-out or presumed-consent policies for organ donation
		CKD	• Provide affordable and sustainable access to basic medications for CKD, diabetes and hypertension and so reduce burden of end-stage kidney disease	
		ESKD	• Devise innovative ways to deliver cheaper dialysis worldwide	
		Transplantation	• Promote safe and altruistic kidney donation by living donors. Improve supply from deceased donors where permissible. Stop organ trafficking	
3.c	Substantially increase health financing and the recruitment, development, training and retention of the health workforce in developing countries, especially in least developed countries and small island developing states	Kidney disease awareness and capacity to treat	• Improve awareness and capacity to diagnose, prevent and treat kidney disease • Train and retain health-care workers with knowledge of kidney disease	Development of innovative financing models to reduce costs of dialysis and transplantation Promotion of the education, licensing and registration of health-care workers and researchers Promotion of the fair remuneration of health-care workers Legislation to define the scope of practice of community health workers and any associated task shifting
3.d	Strengthen the capacity of all countries, in particular developing countries, for early warning, risk reduction and management of national and global health risks	Crush syndrome CKD	• Improve disaster planning and responses to earthquakes and other major disasters • Promote peace • Prevention of wars should reduce both the burden of kidney disease associated with low birth weight and malnutrition and the conflict-related disruption of care	Promotion of international collaboration to respond to natural disasters Commitment to equality and peace Promotion of democracy Strengthening of intersectoral communication and collaboration

AIDS: acquired immunodeficiency syndrome; AKI: acute kidney injury; CKD: chronic kidney disease; ESKD; end-stage kidney disease; FCTC: Framework Convention on Tobacco Control; HIV: human immunodeficiency virus; HUS: haemolytic uraemic syndrome; TRIPS: Trade-related Aspects of Intellectual Property Rights; UHC: universal health coverage; WHO: World Health Organization.

Interpretation:

Papers 3 and 4 take a very concrete approach to prevention of kidney disease. In *Paper 3* the approach was to try to estimate the burden of kidney disease attributable to each risk factor. Risk factors were identified through literature search and consensus within an expert group. Strategies for primary and secondary prevention and advocacy messaging were highlighted for each risk factor. The novelty of this paper was the comprehensiveness of this approach. In *Paper 4* the goal was to illustrate the necessity of multi-sectoral co-operation and collaboration for health, using the example of kidney disease, which lends itself well to this given that it is impacted by many structural and environmental factors. The message of the SDGs is the need for a "health in all policies" approach such that "no one is left behind".[73] Highlighting the potential health benefits of achieving the non-health focused SGDs across the spectrum of kidney disease is novel, and is intended to be a practical illustration of the value of this approach.

It is likely that policy makers are generally aware of the broad concepts outlined in Chapter 3, which apply to many NCDs. This knowledge has however thus far not translated into much action.[12] It is well recognized that over the past 2 decades only 2% of development aid has been directed to NCDs, and kidney disease has not been on the priority list.[13,74] Numbers and data therefore have not been enough to motivate a change in resource allocation or tangible prioritization of NCDs. There are many possible reasons why NCDs as a whole have been relatively neglected, in part due to the higher profile of diseases such as HIV, malaria and tuberculosis, but also the silent comprehension that there is no quick fix for NCDs. NCDs require strong health systems, horizontal integrated disease management programmes and sustained attention. It could be argued that kidney disease is an extreme example of the complexity of managing NCDs, given that it is amenable to prevention, can be controlled for prolonged periods if managed appropriately and continuously, in conjunction with other comorbidities such as diabetes or cardiovascular disease, but requires very high-cost care if kidney failure ensues. As discussed in the introduction, kidney disease also affects large numbers of people and therefore cannot justifiably be left behind.

CHAPTER 4. Approaching the ethical challenges associated with dialysis in resource-limited settings

From a purely utilitarian perspective, dialysis is never cost-effective, even in the richest of health systems.[37,75] However, the egalitarian perspective of providing dialysis to all, at a high cost, under some form of UHC, has prevailed in most high and some middle-income countries as society has not been comfortable with the notion of abandoning patients who require dialysis, and thus allowing them to die.[39] This circumstance has led to exponential growth in numbers of patients receiving dialysis in HICs and to a flourishing dialysis industry. The reality in most lower income settings reflects the conflict between these 2 ethical positions. True universal coverage of dialysis, accessible to all, is rarely possible because of the high dialysis and opportunity costs. Under such circumstances dialysis provision usually begins in the private sector, most often in large urban centers, available to those who can pay, and therefore only for a privileged few. In some LMICs governments try to provide some dialysis but this rarely meets the clinical need or protects individuals against significant CHE. These circumstances exacerbate existing inequities in terms of access to care and create many moral dilemmas for patients, families and physicians as well as for policy makers. These ethical dilemmas are discussed in *Paper 5*. If no policies are in place regarding access to dialysis, disadvantaged and vulnerable patients are *de facto* being abandoned by the health system whether this is admitted or not. How governments can and should approach the "problem" of provision of dialysis within their health systems and their budgets is unclear. There are a limited number of policy options that can be pursued in terms of dialysis provision. These options are discussed in *Paper 5* in the context of their impact on patients, society and the health system.

Transparency and accountability are core elements of policy making. Countries such as Thailand have recently set an example of performing thorough health technology assessments (HTA), eliciting policy maker and societal values and engaging with multiple stakeholders prior to deciding to include RRT under UHC.[76] Ongoing monitoring and evaluation is required after policy implementation to determine whether the intended goals have been reached, whether there have been unanticipated harms and to identify the need for policy revision. Implementation research (IR) is gaining prominence as the most appropriate way to investigate how best to get known effective health interventions into practice and scaled up in low resource settings. A

broad approach to the ethical implications of the planning, implementation and post-implementation processes of IR is outlined in *Paper 6*. These ethical considerations are highly relevant to policy development and implementation, and could be extrapolated to a deliberate and iterative policy making process regarding dialysis as countries progress towards UHC which over time may include dialysis.

PAPER 5

ETHICAL CHALLENGES IN THE PROVISION OF DIALYSIS IN RESOURCE-CONSTRAINED ENVIRONMENTS

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Ethical Challenges in the Provision of Dialysis in Resource-Constrained Environments

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Summary: The number of patients requiring dialysis by 2030 is projected to double worldwide, with the largest increase expected in low- and middle-income countries (LMICs). Dialysis is seldom considered a high priority by health care funders, consequently, few LMICs develop policies regarding dialysis allocation. Dialysis facilities may exist, but access remains highly inequitable in LMICs. High out-of-pocket payments make dialysis unsustainable and plunge many families into poverty. Patients, families, and clinicians suffer significant emotional and moral distress from daily life-and-death decisions imposed by dialysis. The health system's obligation to provide financial risk protection is an important component of global and national strategies to achieve universal health coverage. An ethical imperative therefore exists to develop transparent dialysis priority-setting guidelines to facilitate public understanding and acceptance of the realistic limits within the health system, and facilitate fair allocation of scarce resources. In this article, we present ethical challenges faced by patients, families, clinicians, and policy makers where dialysis is not universally accessible and discuss the potential ethical consequences of various dialysis allocation strategies. Finally, we suggest an ethical framework for use in policy development for priority setting of dialysis care. The accountability for reasonableness framework is proposed as a procedurally fair decision-making, priority-setting process.
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Chronic kidney disease (CKD) mortality increased by 82% between 1990 and 2013, with CKD being one of a few diseases worldwide in which mortality failed to decrease.[1] The true prevalence of acute kidney injury (AKI) and CKD in most low- and middle-income countries (LMICs) are unknown, but are likely at least as high as in high-income countries (HIC).[2–4] Because the symptoms are nonspecific until advanced stages of the disease and awareness and diagnostic possibilities in many LMICs are poor, early diagnosis of kidney disease, when simple interventions could be effective, is often missed. Social determinants play an important role in the risk for kidney disease and its progression in LMICs as outlined in Table 1. Dialysis and transplantation are the only means of surviving chronic kidney failure. Little is known about the need for dialysis among patients with AKI in LMICs, but AKI tends to be more severe than in HICs, most likely owing to delays in presentation to the hospital, and few patients can afford dialysis.[5,6] For patients with end-stage kidney disease (ESKD), the global country prevalence of dialysis ranges from 0.1 (or zero) to more than 2,000 per million population (pmp), showing a vast inequity in dialysis access.[7] The global need for dialysis is projected to double by 2030, largely in LMICs.[8] Recent estimates have suggested that 2.3 to 3.2 million people die annually because of an inability to access dialysis or sustain the treatment.[8,9]

Many ethical dilemmas are raised by the facts that the global burden of renal disease remains undefined, access to early diagnosis and effective management is suboptimal, access to life-saving renal replacement therapy (RRT; dialysis or transplantation) is highly inequitable, and the costs of RRT are prohibitive for individuals and health systems in LMICs. Technology has a global reach, but in LMICs given the costs and infrastructure required, demand outstrips the capacity for equitable access, aggravated by the lack of clear policies about allocation of limited dialysis resources. Thus, priority-setting dilemmas regarding RRT under resource-limited conditions must be addressed: should lines be drawn on

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Table 1. Differences in Kidney Disease Between High- and Low-Income Countries

Countries	Acute Kidney Injury		End-Stage Kidney Disease	
	HIC	LMIC	HIC	LMIC
General mean age (y)	>60	25-50	>60	20-50
Location	Hospital acquired	Community acquired	Community, acquired	Community, acquired
Most common risk factors	Age, CKD, infections, nephrotoxins, surgery	Volume depletion, infections, nephrotoxins, pregnancy	Diabetes, hypertension, glomerulonephritis	Glomerulonephritis, hypertension, HIV, environmental exposures, diabetes, unknown
Multimorbidity	Often present	Often absent	Often present	Often absent
Access to dialysis	Yes	Limited	Yes	Limited
Financing dialysis	State, insurance	Often out of pocket	State, insurance	Often out of pocket
Financing medication	State, insurance	Often out of pocket	State, insurance	Often out of pocket
Preventive strategies	Increased awareness, avoid hypotension, avoid nephrotoxins	Increased awareness, reduce infection rates, vaccinations, reliable availability of antibiotics and intravenous fluids, reduce use of traditional remedies, improve antenatal and maternal care, gender equality, reduce poverty	Increased awareness, early detection and treatment, manage blood pressure, diabetes, obesity, cardiovascular risk factors	Increased awareness; improve access to early detection and essential medications; reduce infection rates; reduce use of traditional remedies; manage blood pressure, diabetes, and HIV; reduce poverty; improve nutrition; improve gender equality, education, and work conditions; reduce environmental exposures

Abbreviation: HIV, human immunodeficiency virus.
Data from Mehta et al[2] and Jha et al.[88]

whom to treat; how patients who should be dialyzed can be dialyzed; and if patients are dialyzed, how much self-payment, if any, is acceptable?

In this article, we use country examples derived from the literature and our experience to highlight ethical concerns and dilemmas at the patient/family, health-provider, and policy-making levels that relate to the treatment of renal failure in LMICs where dialysis is not universally accessible. By using the four ethical principles of justice, beneficence, nonmaleficence, and autonomy, we systematize some potential ethical consequences of four possible RRT policy strategies and suggest ethical frameworks for use in policy development and fair decision making regarding priority setting relating to RRT. For simplicity, the discussion will be limited to dialysis as it relates to both AKI and ESKD because this is the predominant form of RRT in most LMICs. The ethical challenges surrounding transplantation and access to diagnosis and primary and secondary prevention of kidney disease are discussed elsewhere.[3,10–15]

ACCESS TO DIALYSIS IN LMICS

In LMICs, the clinical problem of kidney disease is aggravated by a lack of awareness among communities and health care workers (HCWs) of the risk and seriousness of the disease, and limited diagnostic facilities.[14] Even among patients who are diagnosed, the mortality from AKI and ESKD is high because of many barriers to dialysis access.[6,8,13,16,17] Provision of dialysis varies between regions and countries, from universal access in some Latin American countries to none in many Asian and sub-Saharan African countries.[18,19] Dialysis access in LMICs mainly, but not exclusively, is a function of economics. In general, more prosperous nations can afford more, and dialysis rates are highest in countries with universal health coverage (UHC).[18,19] Some Latin American countries, however, have committed themselves to universal dialysis coverage despite lower health expenditures, indicating the political will to provide financial risk protection from kidney disease, which is a health priority in the region.[19] In sub-Saharan Africa very few countries have dialysis facilities, and where these are available few have policies in place regarding access to dialysis.

Policy makers are hesitant to address the controversial topic of how limited dialysis resources should be allocated. Much of the dialysis in LMICs currently is delivered in the private sector and high out-of-pocket (OOP) costs often lead to financial ruin of the family, discontinuation of treatment, and death once resources are exhausted.[6,16,20,21] Even when funded or subsidized by governments, dialysis facilities in LMICs tend to be located in cities, often are small, have poorly maintained equipment (at times donated by well-wishers without adequate technologic support), have frequent staff and stock shortages, and unreliable water and electricity supplies, and therefore struggle to meet the clinical need.[12,22–24] Even in the few state-supported facilities access to dialysis is haphazard and inequitable in the absence of formalized guidelines, and the burden of choosing between life and death is borne by individual patients, families, and clinicians, causing significant emotional and moral distress.

Affordability of Dialysis in LMICs

Advocacy is mounting globally for universal access to dialysis for AKI because it is anticipated to be life-saving but temporary (and therefore to cost much less than life-long treatment for ESKD).[2] The costs associated with dialysis for AKI in LMICs, however, often remain prohibitive; for example, 5 days of dialysis for a child in Nigeria costs several times the monthly minimum wage.[6] In some countries (eg, Ghana, Tanzania, and Nigeria), short-term dialysis for AKI is included under national health insurance schemes, in-patient government-funded services, or is funded by non-governmental organizations (NGOs).[25–28] Under these circumstances, however, if a patient fails to recover kidney function or requires longer treatment, the OOP costs become unaffordable and dialysis actively must be discontinued.[25–27] In India, dialysis may be provided free of charge in some government-funded hospitals, but patients must purchase medications and disposables, the cost of which often is prohibitive.[29] Certain governments or charities (eg, Guinea, Cameroon, Senegal, and India) substantially subsidize the cost of chronic dialysis, and OOP costs may be reduced to US $2.30 per day for peritoneal dialysis (PD) and US $1.50 to $3.20 for a hemodialysis (HD) session, depending on the country.[30–32] Even these prices generally are unaffordable long term, however, and often exclude the costs of transportation, medications, or account for time lost at work.[20,29,33] Protection from financial risk is therefore an important consideration in reducing inequitable access to dialysis worldwide.

THE EVOLUTION OF ETHICAL CHALLENGES IN DIALYSIS ACCESS

Dilemma of Distributive Justice

When HD first was introduced as a treatment for ESKD in the 1960s, access was restricted severely because of limited availability and high costs. The evolution of ethical challenges imposed by dialysis in the United States, the first country to provide chronic HD, likely mirrors the experience of most countries.[34] Initially, existing resources failed to meet the clinical

need. Dialysis was more accessible to patients would could pay OOP, but fair allocation of the few existing dialysis slots was difficult.[34] Rationing decisions were made by a small group of individuals, colloquially known the "Life or Death Committee."[35] Case-by-case decisions were based on the members' consciences and a patient's perceived social worth, rather than any firm philosophical or ethical principles. Reporting of this rationing process in the media led to a public outcry and after much lobbying and advocacy, the Social Security Amendment Act was passed in 1972, under which all ESKD patients would receive Medicare benefits and gain access to dialysis.[35,36] This was a contentious, complex decision.[36,37]

Since the US establishment of chronic dialysis programs, HICs have progressed to supporting universal access to dialysis at varying rates. Throughout the evolution of dialysis, however, as the technical, cost, and access barriers progressively were overcome, the demand for dialysis and the budgets have escalated considerably beyond expectation.[13] Approximately 2% of national health care budgets in HICs are spent on ESKD, which impacts less than 0.2% of the population.[13] The disproportionately high costs of ESKD when compared with costs for other diseases that may affect larger numbers of people now are bringing the ethical challenges of dialysis full circle back toward justice and fairness of resource allocation as sustainability questions for growing ESKD programs are raised.[34,38,39]

Trade-Offs Between Beneficence and Nonmaleficence

Despite the concern of increasing costs, in HICs people now rarely die of renal failure, instead they die with renal failure, on dialysis, from other comorbidities.[34,40] Given the technical advances in health care the question now no longer is whether we can keep people alive, but at times whether we should: whether we are truly improving quality or merely quantity of life?[40,41] In recognition of the fact that quality of life on dialysis may not always be optimal, there is an increasing awareness that comprehensive supportive care may be a superior alternative, especially for older ESKD patients.[40] In LMICs, however, patients needing dialysis are younger and otherwise generally healthy (Table 1), and therefore lack of access to dialysis clearly leads to harm.

Dilemma of Respecting Patient Autonomy

Bioethics in HICs focus strongly on preserving patient autonomy, given that individual patient decisions are unlikely to impose major opportunity costs on the broader health system.[42] Since cost restrictions on dialysis were lifted, individual patient autonomy has been the over-riding ethical principle in determining whether dialysis is initiated or not. This luxury of patient choice, however, largely is attainable only in settings where dialysis costs are covered through UHC or insurance schemes. In lower-income settings, patients paying OOP cannot truly be considered to have autonomy because explicit or implicit rationing or personal circumstances may impose a decision against the patient's will.

ETHICAL CHALLENGES FROM THE PATIENT/FAMILY PERSPECTIVE

Most patients who develop AKI or ESKD in LMICs are younger, economically active, and may be the family's sole breadwinner.[6,28,43,44] Patients often present late with profound uremia as the first clinical presentation of kidney disease.[6,16] Women and children generally are under-represented, likely owing to their low economic power.[20,25,45,46] The decision to seek care for kidney failure is complex. As outlined in Figure 1, the patient/family/HCW are required to make multiple resource-dependent decisions that ultimately impact survival.[6] The search for resources involves use of a family's own funds, sale of property, and incurring debts, yet with no guarantee of survival.[16,47–49] In Thailand, before ESKD was included under UHC, some households used up to 74% of their income to sustain a single family member on dialysis.[50] Families coped by reducing dialysis frequency and reducing food, education, and other expenditures. This study was pivotal in informing Thai policy on extending dialysis to the whole population to protect families from financial risk.[50] In patients with ESKD a cost-benefit thought processes occurs before each dialysis session and imposes significant moral dilemmas as choices are made on how to allocate the meager household resources, often at the expense of other family members' needs.

Given that most patients who commence dialysis in LMICs where OOP payments are required discontinue after a few sessions, the question arises as to how well patients realize the full implications of dialysis. Many studies from India and Africa have shown that despite patients being fully informed about ongoing costs required, only a small proportion of patients can sustain even short-term dialysis.[6,16,51] Patients and families initially are desperate to preserve life, but soon "reality dawns and emotions and resources are exhausted" and the family must contend with the loss of a loved one and a deeper descent into poverty.[21] A Nigerian study reported that 27% of households incurred a catastrophic health expenditure (CHE) after an average health expense of US $19.60 in a month.[52] A CHE is defined as an expense that risks or sends a household into, or further into, poverty or household

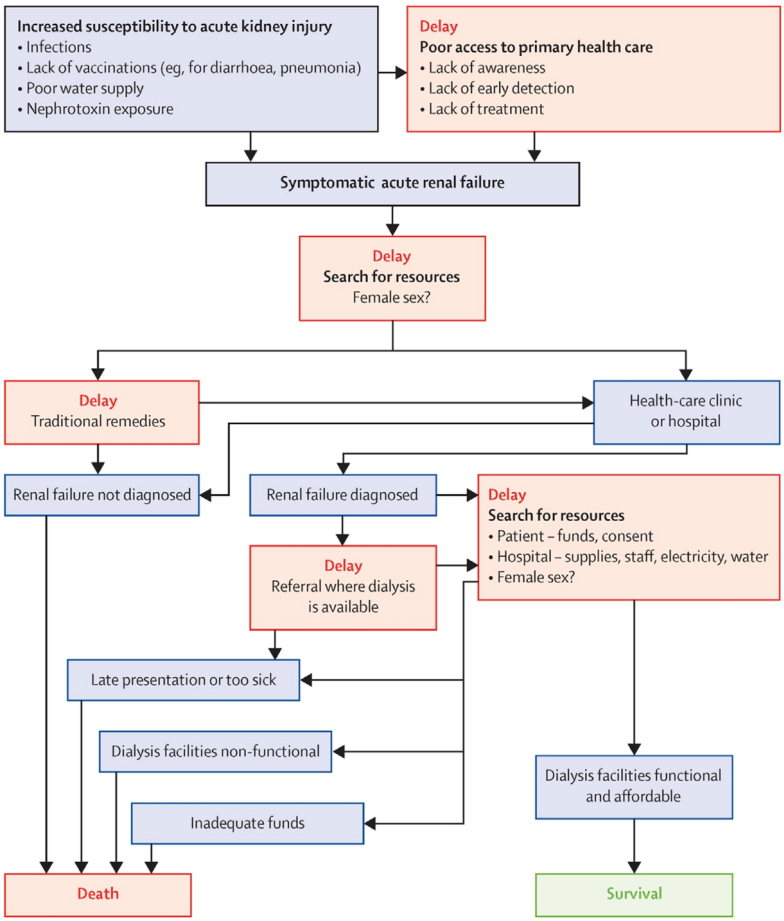

Figure 1. Barriers to care in AKI. Outcomes shown for each pathway (survival or death) are the most likely outcomes, but are not inevitable. Copyright © 2016 Olowu et al. Open Access article.

OOP in excess of 40% of household income after covering the cost of basic needs.[53–55] The majority of households in Nigeria therefore would experience CHE from one dialysis session, which costs approximately US $150.[51] An Indian study of ESKD patients referred for transplantation found that 72% experienced some form of financial crisis as a consequence.[49] Of concern, more than 10% of patients on the eve of transplant regretted embarking on such expensive treatment and said they would not do it again given the choice.[49] These data underscore the urgent need for financial risk protection for patients with ESKD.[56]

Many studies from LMICs report a significant proportion of patients with AKI or ESKD disappearing and leaving the hospital against medical advice.[6,16,57] This is often a desperate act when families realize they are faced with the impossible choice of paying for care or letting their loved one die. A sense of shame likely accompanies many of these decisions. The ethical dilemma of parents declining life-saving dialysis for children in LMICs is very different from that in Western countries where, at times, physicians appeal to the courts to enforce treatment for a child when a parent refuses.[58,59] Parents in LMICs attempt to act in the best interest of the child; however, once a decision must be made about a catastrophically expensive treatment, they must weigh their own and the rest of the family's livelihoods against that of the sick child. Such choices create much distress and anxiety, the long-term impact of which remains unknown.[47,60]

ETHICAL CHALLENGES OF DIALYSIS AT THE CLINICAL LEVEL

An analysis of factors limiting access to dialysis among children in Nigeria reported that despite 33 of 51 families being willing to pay, only six children received dialysis.[22] The majority did not receive dialysis because of a malfunction or lack of dialysis equipment (22 children), shortage of staff (3 children), or the staff being reluctant to dialyze for fear of impoverishing the family (3 children).[22] Both material and human resources are important factors restricting access to dialysis in LMICs. Ethiopia, for example, has

approximately 100 million inhabitants but has only three pediatric and nine adult nephrologists, providing a nephrologist to population ratio of 0.12 pmp. The average ratio in Europe is approximately 20 pmp.[61] Measurement of serum creatinine is not always possible outside of cities. If a patient requires dialysis the only option is referral to Addis Ababa or a few other towns, and most costs are OOP (Table 2). There are presently 15 HD units providing dialysis in Ethiopia. Acute PD recently was initiated in one public hospital but there is no chronic PD. There are 115 HD machines in the whole country, 24 of which belong to the public sector, mainly providing acute dialysis. There are 356 patients on chronic HD, of which only 8 are in the public sector. Most patients are dialyzed once or twice weekly (A.M.E.). The internationally recommended HD dose is 4 hours, three times a week.

When resources are available but limited, HCWs often struggle to balance the conflicting roles of advocating for the patient and protecting the hospitals' resources.[62] A recent nationwide survey of 587 Ethiopian physicians investigated the toll of moral distress imposed by this conflict, which is outlined in Table 3.[62] Most agreed there was a lack of official guidance on allocation of available resources and the first-come, first-served strategy was used most commonly.[62] More than 80% of respondents reported that in the prior 6 months they had been unable to obtain dialysis for patients in need. Half of the physicians reported consciously considering the hospital's costs when screening patients for dialysis.[62] The lack of explicit rationing guidelines leads to such implicit case-by-case rationing, which is highly variable and exacerbates inequities between patients with similar needs.[63] This underscores the ethical imperative for the development of explicit and transparent guidelines to reduce this variability and reduce the moral distress experienced by HCWs.[63]

Reduction of Quality of Care as a Survival Technique?

In many LMICs, once a patient commences dialysis further ethical challenges arise in clinical management either because of limited institutional resources or the patient's ability to pay. Clinicians agonize over deliberately providing suboptimal dialysis by restricting the duration or frequency of HD, reducing the number of

Table 2. Ethiopian Dialysis Costs

Item	Cost[89]
Public hospital dialysis*	
AKI	Free for 1 month
ESKD–poorest population segment	Not available†
ESKD–others (OOP)	$23 per HD session
Venous catheter for first dialysis session (OOP)	$46
Transport, syringes, diagnostic testing, medications (OOP)	Extra costs as required
Private hospital dialysis	
HD, AKI, and ESKD (OOP)	$68 per session ($10,680/y)
First dialysis session including catheter, procedures, tests (OOP)	$137-$228
Arteriovenous fistula (OOP)	$365-$456
Additional costs (OOP)	Average $182
Creatinine measurement	
Hemoglobin measurement	
Calcium, phosphate measurement	
Erythropoietin	
Intravenous iron	
1 month of blood pressure medication	
Travel to and from dialysis within the city	
Transplant surgery (OOP)	
Including 1 week pretransplant and 2 weeks post-transplant in India and transport costs	$20,000
For comparison	
Specialist physician working full time in government hospital	$456 per month
Manual worker in rural/semi-urban area around the capital	$45 per month
Per capita health expenditure Ethiopia (2013)‡	$25 per person per year
Earnings below poverty line poverty-line (≤%1.25/d)	44% of the population
Out-of-pocket expenditures on health (National Health Account Ethiopia 2014)	34% for adult interventions 48% for child interventions

Data in Table 2 are from a personal communication with AME.
*Only available in selected public hospitals.
†Except for very few awaiting kidney transplantation in one center.
‡WHO global health observatory data repository.

Table 3. Proportions of Ethiopian Physicians Experiencing Resource-Related Dilemmas

Rationing dilemmas	Often (%)	Sometimes (%)	Rarely (%)	Never (%)	NA (%)	Total
Limitation of resources required me to make a difficult choice	55	39	5	1	0	551
The preferred course of treatment was not pursued because of a patient's ability to pay	40	43	12	5	0	547
There was significant disagreement among health care personnel on continuing treatment of the patient due to lack of resources	19	38	30	11	2	541
You felt that the patient's need of treatment was not in agreement with the patient's family needs or welfare	13	48	29	8	2	549
You were restricting treatment to a patient to give those resources to someone who could benefit more (i.e. hospital bed, ventilator, medication)	14	32	18	33	3	538

Adapted from Defaye et al[62] under the Creative Commons License (http://creativecommons.org/licenses/by/4.0/) with additional unpublished data (Miljeteig et al, unpublished data).

daily PD exchanges, use of temporary catheters long term to reduce costs, and knowing patients cannot afford the medication required (eg, erythropoietin).[12,16,22,29,51,64–66] Recent debate has considered whether it is ethically acceptable to provide less-effective medication to more people for certain diseases (eg, human immunodeficiency virus), rather than restricting more expensive state-of-the-art medication to fewer people.[67] On balance, it would seem less harmful overall to treat more patients with an acceptable second-line treatment rather than fewer patients with a first-line regimen.[67] Such an approach may be feasible when the choice of medication can be adapted safely within a budget to achieve the desired amount of coverage. This reasoning, however, cannot be extrapolated easily to dialysis. Dialysis resources are much more limited and less divisible and therefore there is less room for compromise, and outcomes of any such strategy would need to be monitored closely.

In Sudan, all patients who present with kidney failure are offered dialysis.[23,68] To accommodate as many people as possible, chronic HD is offered for 4 hours twice a week, knowing that patients will be underdialyzed.[23,64,69] Evaluation of the program found that patients with clinical indications, such as volume overload, and more children in practice received dialysis three times a week.[69] The Sudanese therefore have taken an egalitarian approach to maximize the number of people treated, but those who are worse off or children may be prioritized further. This approach, which also is used in other LMICs to reduce patient costs, is ethically defensible based on the principle of justice and financial risk protection, but the major concern is whether there may be a risk of systematic harm related to underdialysis.[29,31,33,70,71]

When the HD dose is reduced to twice a week, if dialysis continues regularly as in Sudan and in China, survival and quality of life may be acceptable; this compromise appears feasible.[69,72] In practice, however, further reducing dialysis frequency is common among patients who struggle to remain alive with limited resources.[16,29,50] The majority of patients cannot continue for more than a few sessions, a trend that has not improved despite the growing number of dialysis units in many LMICs.[6,16,28,51] The role of the HCW beyond ensuring fully informed consent, in restricting access to dialysis if it is clear the patient's resources are insufficient to sustain reasonable health, is unclear. Some programs only accept patients for long-term dialysis if they are able to make several months' prepayment, which may be a practical strategy to reduce CHEs and an attempt to ensure sustainability.

One could argue that focusing on the quality of dialysis may not be relevant in practice when the only actual choice is between any dialysis (life) and no dialysis.[1] Ethically, however, it is questionable whether there is, or should be, a minimum standard for dialysis, and whether this is a determination that the state, physician, or patient should make.[21] In LMICs, a patient's choosing to dialyze infrequently, based on being less worse off when receiving poor dialysis compared with no dialysis, is an exercise of their autonomy. However, this presents a challenge for the HCWs and may impact other patients. HCWs cannot control how often a patient comes for dialysis or their access to medication and therefore may feel helpless and frustrated when confronted with the ongoing deterioration of a patient's condition.[66]

There are, therefore, many dilemmas faced by HCWs caring for patients with kidney disease in LMICs. In the Ethiopian physician study described earlier, 88% of physicians were so troubled by the lack of resources that they had daily or weekly regrets about their choice of profession.[62] It is likely that many of these challenges drive the brain drain of health professionals from LMICs to better-resourced countries. The potential impact on the entire health system therefore is significant.

ETHICAL CHALLENGES OF DIALYSIS FROM THE HEALTH SYSTEMS/POLICY PERSPECTIVE

The Challenge of Priority Setting

UHC is defined by the World Health Organization as "all people receiving quality health services that meet their needs without being exposed to financial hardship in paying for the services."[73] In addition, there is a growing realization that the right to health may be considered fundamental in the realization of global human rights.[74] At first glance it therefore would seem consistent with these goals that dialysis treatment for patients with kidney failure is a human right and should be covered under UHC. The reality, however, is that every health system has a limited budget, much more constrained in LMICs than in HICs, and entitlement to the fulfillment of an individual's right to health must be balanced against the resources available and respect the concept of fairness to other individuals.[74,75] The three core goals of UHC are to expand priority health services, to extend health coverage to more people, and to reduce financial hardship as a consequence of seeking health care.[73] The realization of human rights also involves addressing the social and structural determinants of health including poverty, education, gender equity, safety, and infrastructure. Policy makers therefore are faced with the difficult task of determining which conditions should have priority and why, and how to allocate resources. Important trade-offs must be considered between implementing strategies that maximize aggregate population health and those that specifically address the needs of the worst off patients.[74]

Patients with kidney failure are dying because of a lack of access to treatment; however, the costs of treatment for a single patient per year may be several hundred times the individual per-capita health expenditure of a country, and many times the per-capita income per year.[76] The opportunity costs of dialysis therefore are extremely high in terms of financial costs and lives lost. In many LMICs, basic and highly cost-effective health services such as skilled birth attendance or treatment of childhood pneumonia or diarrhea are not available for the majority of the population. Cost effectiveness in terms of quality-adjusted life-years gained per dollar is a major concern for policy makers when comparing and prioritizing interventions in designing essential health care packages. The development of kidney disease, however, may in part be the result of poor public health practices and the lack of UHC or other structural factors, and the state could be considered partly responsible. In addition, vertical equity demands that patients should have access to treatment according to their needs. The views on state assistance for dialysis in LMICs, however, are very divergent. Some experts consider provision of coverage for dialysis to be an "unacceptable trade-off[73]" in a health system in which UHC and meeting more urgent health needs have yet to reach all individuals.[75] Others have suggested that patients with kidney failure can be considered worse off because they would die imminently without dialysis and almost universally experience catastrophic financial hardship by paying OOP.[38,50] Viewed through the lens of distributive justice, however, as a compromise, the possibility of rationing expensive therapies may be necessary. Rationales underlying potential fair strategies for rationing the scarce resources are expertly reviewed elsewhere.[70] In all cases, clear and transparent policies are needed to allocate scarce resources and ensure delivery of fair and appropriate care. Restrictive policy thresholds governing access to dialysis may be acceptable to the population if the policy-making process is clear and transparent and fosters public trust in the governance process.

Framework and Methodology to Support Decision Making for Fair Distribution of Resources

Marckmann et al[77] have proposed a practical transparent ethical framework for public health policy making based on ethical foundations. Underlying this framework is the recognition that public health policy making should be systematic, transparent, consistent, and ethically justifiable.[77] They chose to base their approach on the coherenist ethical principles of justice, beneficence, nonmaleficence, and autonomy in contrast to using the more polarizing ethical frameworks of utilitarianism/egalitarianism or favoring the worst off.[77] Their approach begins with the consideration of 5 normative criteria (Table 4): anticipated improvements in the health of the target population; possible negative consequences; autonomy implications; equity implications; and the anticipated efficiency in terms of cost effectiveness, which are a prerequisite to build ethical justification for a decision-making process.[77] In Table 4 we present a crude analysis of ethical considerations raised under these five criteria as they relate to four possible dialysis allocation strategies: state provision of dialysis for all, state provision of dialysis for AKI only, state rationing of dialysis, or no state coverage of dialysis. This analysis is not comprehensive and we do not suggest which strategy would be most appropriate under specific circumstances. This rudimentary analysis, however, can be a starting point for transparent discussions by policy makers and other stakeholders involved in decisions regarding implementing or scaling-up dialysis. The depth and breadth of discussions then must be tailored to the relevant contexts.

Table 4. Potential Ethical Challenges Raised by Four Possible Policy Strategies for Universal Coverage of Dialysis in LMICs

Policy Strategies	Normative Criteria Underlying Ethical Justification				
	Expected Health Benefits for Patients Requiring Dialysis (Beneficence)	**Potential Harm or Burdens to the Individual and to the Health System (Nonmaleficence)**	**Impact on Individual Patient Choice (Autonomy)**	**Impact on Equity (Justice)**	**Expected Efficiency (Cost Effectiveness)**
Universal coverage of dialysis for all patients with AKI and ESKD	Decreased mortality and morbidity[6,38] Improved quality of life Increased productivity because patients should be able to work and support their families Healthier patients survive longer, may receive transplants that improve survival	High total and opportunity costs of dialysis Inequity and unfairness within health system (if other conditions are not covered)[90] Geographic/other barriers may persist Cost-saving strategies may reduce dialysis quality (less reduction of mortality and morbidity) OOP for medication, transportation, re-location may remain high and prohibitive[91] Unanticipated escalation of costs if costs not contained up front[38] May reduce overall expenditure on public health and prevention[92]	Respects patient autonomy Respects HCW autonomy to act as they believe is required, reduces moral distress	Protection of renal patients/families from CHE[50] Improves equity among patients with renal disease May exacerbate inequity between patients with renal disease and other conditions that may not be covered[90] May exacerbate inequity between urban and rural populations[23,91] Inequities among renal patients still may remain if gender, religious, ethnic, social barriers, or high OOP costs for medication and transport, lost wages reduce access to dialysis Inequitable access to diagnosis of renal failure will translate into inequities in receiving dialysis if needed	Dialysis for ESKD is not cost effective compared with many other treatments[38,95] Limited data on cost effectiveness of dialysis for AKI Requires sustainable infrastructure (diagnosis, facilities, supplies, and skilled HCWs) Often saves/prolongs lives of bread winners, contributing to economic growth Often saves/prolongs lives of adults who care for others May reduce brain-drain because HCWs may be encouraged Survival to transition to transplantation is cost effective
Universal coverage for AKI only (limited cost because of anticipate renal recovery, limited coverage under national health insurance for those enrolled)	Decreased mortality and morbidity for AKI patients[6,38] May increase awareness of AKI, which may improve prevention/early detection	No health benefit for ESKD patients OOP costs for medication, transfusions, loss of work for accompanying caregivers may remain high[91] High opportunity costs of dialysis in some health systems Inequity within health system[90] May still be barriers, unanticipated cost escalations[38] Potentially reduced funds for public health and prevention[92] If coverage only permits a limited number of treatments this may pose dilemmas if AKI patients do not recover within the covered time period (or if ESKD was misdiagnosed as AKI) High OOP and potential CHE for families deciding to continue treatment elsewhere Moral distress for clinicians withholding dialysis from ESKD If AKI policies rely on NGOs or outside drivers initially, sustainability over the long term may not be guaranteed	Respects autonomy in patients with AKI Denies autonomy to patients with ESKD Restricts HCW autonomy to treat only AKI	Protection of AKI patient from CHE Improves equity among AKI patients Will exacerbate inequity between AKI and ESKD May exacerbate inequity renal disease and other conditions not covered[90] May exacerbate inequity between urban and rural populations[93] Inequities still may remain if other barriers to accessing health remain (sex, social, ethnicity, age) Relies on equitable and appropriate access to diagnosis of AKI	More data are required on cost effectiveness of dialysis for AKI Likely less cost effective than other interventions (eg, prevention, early diagnosis, and treatment) Some countries support limited dialysis sessions for AKI, which may not be enough in certain cases[25,28] Requires significant, but sustainable, infrastructure (less for PD) Probably less cost effective than many other interventions (including prevention of AKI) Often save lives of economically active individuals caring for others

Table 4 (*continued*)

Policy Strategies	Normative Criteria Underlying Ethical Justification				
	Expected Health Benefits for Patients Requiring Dialysis (Beneficence)	**Potential Harm or Burdens to the Individual and to the Health System (Nonmaleficence)**	**Impact on Individual Patient Choice (Autonomy)**	**Impact on Equity (Justice)**	**Expected Efficiency (Cost Effectiveness)**
State coverage under limited conditions (rationing, reduced dialysis dose, state subsidy for dialysis)	Decreased mortality and morbidity for patients accepted for dialysis Health may be suboptimal if dialysis is delivered at a reduced dose Decreased mortality and morbidity for patients able to pay subsidy long term	Higher risk of CHE for patients not included State subsidy even if high still may be prohibitive[30,32,71] High opportunity costs even of limited dialysis Justice issues within health system if other expensive treatments are not covered[90] Moral distress of patients, families, and health care workers when withholding treatment[84,85] Still may be barriers, unanticipated escalation of costs[38] Possibly reduced funds for public health and prevention[92]	Patient autonomy not prioritized[85] Restricts HCW autonomy	Protection of those accepted for dialysis from CHE Increases inequity between patients accepted/not accepted for dialysis May exacerbate inequity of renal disease and conditions not covered[90] Inequities still may remain if gender, religious, ethnic, social, geographic barriers in access to health[84] Relies on equitable access to diagnosis of renal failure	If public funding is used instead for cost-effective interventions it saves lives Attempt to contain costs through rationing or reducing dialysis dose/ frequency May save lives of economically active individuals caring for others More patients may be dialyzed if strategy is to reduce dialysis dose to increase numbers of patients treated
No state coverage (requires a policy rather than ignoring the issue)	Patients without personal resources to pay out of pocket or have health insurance likely die	High risk of CHE, financial risk with no guarantee that life will be saved (likely worse for ESKD versus AKI) Moral distress of patients, families, and HCWs needing to make individual life-and death decisions[62] May contribute to brain drain of HCWs	Patient autonomy not considered HCW autonomy not considered	Highly inequitable between patients able to pay OOP or patients unable to pay May improve justice across population if priority setting is fair[94]	If public funding is used instead for cost-effective interventions it saves more lives[92]

Abbreviations: NGO, non-governmental organization.

Table 5. Application of A4R Framework for Fair Dialysis Policy Making[74]

A4R Condition	Relevance to Dialysis
1. Publicity condition	All decisions and rationales for limiting dialysis availability should be accessible to the public Transparency is crucial Facilitates social learning curve and understanding among public of rationing and rationales
2. Relevance condition	Clear understanding of whether kidney disease is a health priority in the country (numbers affected, numbers at financial risk, potential to meet the needs fairly) Rationale for limiting access to dialysis should be reasonable and clearly explained, acceptable to "fair-minded people" Decisions should be based on accurate data relating to burden of kidney disease, costs, opportunity costs, equity concerns, and potential financial risk Decisions should be reached in collaboration with all relevant stakeholders to enhance legitimacy and understanding (policy makers, health care workers, civil society, and others)
3. Revision and appeals condition	Possibilities to appeal rationing decisions must be available Facilitates iterative learning and adaptation of policies
4. Regulative condition	Regular official evaluation and by the public to ensure all conditions of A4R are met Encourages accountability, social learning of the A4R process

Marckmann et al[77] advocated use of the methodologic approach of Accountability for Reasonableness (A4R) as proposed by Daniels and Sabin[80] in using their framework, which emphasizes fairness in health care priority settings to operationalize their framework.[78,79] The A4R framework is applicable at all levels of decision making in the health system (micro, meso, and macro), and requires that decisions be made based on relevant values, principles, or evidence; includes active stakeholder engagement in a transparent process; and is open to appeals and review mechanisms (Table 5).[74] Unlike other priority setting processes that emphasize what decisions should be made, the A4R framework directs the inquiry at how and why decisions should be made, and therefore is amenable to local adaptation.[81] In Table 5 we broadly outline how A4R may apply to decision making around dialysis. These considerations do not represent a comprehensive analysis and will require further contextualization, but are put forward as important steps required to ensure a fair and legitimate decision-making process.

Use of the Accountability for Reasonableness Framework for Allocation of Dialysis in South Africa

South Africa is a middle-income country and has a two-tiered health system in which dialysis is freely available to the 16% of the population who have private insurance; the remaining 84% are dependent on the state for health care and dialysis.[82] The state provides dialysis for all patients with AKI but rations dialysis for ESKD. The principle of dialysis rationing was tested in the constitutional courts in 1997 when a 41-year-old man with diabetes and heart disease was refused dialysis.[83] The court ruled from a utilitarian perspective that, despite the patient's right to life, the state could not fulfill its other constitutional health responsibilities should it provide dialysis for all.[83] In South Africa at the time, selection of patients for dialysis was performed by committee (as occurred early on in the United States) and followed consensus guidelines proposed by the National Department of Health. The process was unregulated and had no formal accountability or oversight. Upon review of the process clear biases emerged, most disturbing of which was the favoring of white over African patients.[84] In view of the perceived unfairness, the lack of accountability, and the real risk of litigation, the nephrology community decided to review allocation of the scarce resource. A utilitarian approach, rather than prioritization of social justice, was believed more appropriate for the challenges faced. The normative approach, similar to that described by Marckmann et al,[77] based on the HCWs everyday moral values and convictions, was used. Procedurally, the guidelines were developed using the dictates of A4R, based on criteria that were supported wherever possible by relevant local evidence and the prevailing clinical realities. All relevant stakeholders including patients, clinicians, civil society, hospital management, bioethicists, and legal experts were engaged in an iterative process. Criteria were grouped broadly into medical and social categories, which both impacted outcome decisions. The process was lengthy and challenging; draft guidelines underwent numerous iterations and finally were adopted as Western Cape Government policy in 2010.[85] In addition to the guidelines, a hierarchical allocation system also was developed that took resource availability into consideration. The ability of patients to pay was never a consideration. The outcomes of this process currently are under review, however, preliminary

data show that race no longer features in patient selection (MRM, personal communication).

The importance of this approach is that all relevant stakeholders participated in the process, which improves understanding and legitimacy.[80] The guidelines are available to the general public and therefore are transparent.[85] Patients or their families who were aggrieved by decisions were invited to lodge appeals. Health services in South Africa are under increasing pressure and growing numbers of patients with end-stage renal disease were being refused treatment. This resulted in increasing reviews and complaints, including a formal complaint to the Human Rights Commission. Having the policy guidelines in place allowed the Commission to make a no-fault finding against the Western Cape Government. The experience of patients awaiting the decision of whether they are accepted for dialysis or not has not been studied systematically, but is distressing and adequate psychosocial and palliative care support is crucial to navigate this process.[86] Rationing is always challenging, the transparent process at least optimizes fairness and removes the full responsibility of individual life-and-death decisions from doctors and patients at the bedside.

CONCLUSIONS

The ethical dilemmas arising from managing patients with kidney disease in resource-limited environments are many. The current burden of disease and the limited health budgets in LICs make progress in improving universal access to RRT a major challenge.[87] To begin to tackle the ethical challenges, which largely are rooted in poverty and vulnerability, the burden of disease in terms of patient numbers and societal impact must be quantitated. Simultaneously, and to facilitate accurate data collection, education of communities and HCWs about kidney disease as well as up-scaling of diagnostic capacity are crucial. Where dialysis is occurring, cost data and patient outcomes must be tracked to inform priority setting and policy development. Anthropologic studies are required to understand patient and family experiences, their understanding of kidney disease, and the process of decision making regarding seeking care. Potential solutions to the challenges of sustainability and achieving justice for patients with kidney disease will be highly complex and very context-specific. Policy makers must take into account the relevant normative concerns and follow transparent procedures as outlined in A4R to ensure fair decision making regarding provision of dialysis in LMICs. If states choose to support dialysis in some form, clear and fair eligibility criteria must be established. Policy decisions must consider a minimum quality of care that should be mandated within the state support. If state support for dialysis is deemed unaffordable, activities in the private sector still should be monitored to assess the impact of CHE. Policy decisions should be communicated to the public clearly and adequate palliative care facilities should be in place. Provision of guidance and support also should be considered for patients, family members, and HCWs faced with daily dilemmas at the bedside such that respect, dignity, and humanity of all concerned are preserved at all times.

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PAPER 6

DEVELOPING THE ETHICS OF IMPLEMENTATION RESEARCH IN HEALTH

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Developing the ethics of implementation research in health

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Abstract

Implementation research (IR) is growing in recognition as an important generator of practical knowledge that can be translated into health policy. With its aim to answer questions about how to improve access to interventions that have been shown to work but have not reached many of the people who could benefit from them, IR involves a range of particular ethical considerations that have not yet been comprehensively covered in international guidelines on health research ethics. The fundamental ethical principles governing clinical research apply equally in IR, but the application of these principles may differ depending on the IR question, context, and the nature of the proposed intervention. IR questions cover a broad range of topics that focus on improving health system functioning and improving equitable and just access to effective health care interventions. As such, IR designs are flexible and often innovative, and ethical principles cannot simply be extrapolated from their applications in clinical research. Meaningful engagement with all stakeholders including communities and research participants is a fundamental ethical requirement that cuts across all study phases of IR and links most ethical concerns. Careful modification of the informed consent process may be required in IR to permit study of a needed intervention. The risks associated with IR may be difficult to anticipate and may be very context-specific. The benefits of IR may not accrue to the same groups who participate in the research, therefore justifying the risks versus benefits of IR may be ethically challenging. The expectation that knowledge generated through IR should be rapidly translated into health policy and practice necessitates up-front commitments from decision-makers to sustainability and scalability of effective interventions. Greater awareness of the particular ethical implications of the features of IR is urgently needed to facilitate optimal ethical conduct of IR and uniform ethical review.

Introduction

Implementation research (IR) is growing in importance and recognition: there is an increasing funding from a range of donors/sponsors for this research area, leading scientific journals have established sections promoting the publication of such research, and it contributes increasingly to the evidence-base used by the World Health Organization (WHO), which promotes, supports, publishes, and evaluates such research [1]. With its aim to answer questions about how to improve access to interventions that have been shown to work but have not reached many of the people who could benefit from them, IR involves a range of particular ethical considerations that have not yet been comprehensively covered in most international guidelines on health research ethics [2, 3]. The draft of the Council for International Organizations of Medical Sciences (CIOMS) guidelines which is currently under revision as well as its commentary does briefly allude to ethical considerations in the conduct of cluster randomized trials (CRT), but thus far there has been no comprehensive discussion or guideline regarding the application of ethical principles in IR in general or in relation to study designs beyond CRTs [4].

In response to the need for more clarity and guidance about the ethical implications throughout the IR process, Special Programme for Research and Training in Tropical Diseases (TDR) and the Global Health Ethics unit in collaboration with the Alliance for Health Policy and Systems Research at the World Health Organization

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are developing a training tool, the Ethics in Implementation Research Toolkit, as a practical guide for IR researchers and ethics committees to facilitate optimal study design, conduct, and review. The training tool was developed through a consultative process launched in Geneva in which IR experts, philosophers, ethics committee members, and public health practitioners met to identify the ethical issues in IR, define the course content and the format of the training workshops. The tool was further developed through small group work with the support of an expert in adult training methods. The tool has been validated in two pilot workshops in Asia and Africa. The list of experts who contributed to the development of the Toolkit, apart from the authors of this manuscript, can be found in the Acknowledgements section.

This manuscript is constructed around the concepts identified during the development and piloting of the Ethics in Implementation Research Toolkit and aims to highlight the differences in application of ethical principles between clinical and implementation research, and to highlight the current gaps in ethical guidelines for the conduct of IR.

Background

IR involves increasing the understanding of how to improve access to health products and strategies that are already available and have been shown to work, but remain beyond the reach of many of the people who could benefit from them. IR therefore provides the link between what should happen in theory and what actually happens in practice. It is rooted in the identification of practical problems facing disease control programmes and in finding solutions which improve access to health interventions and lead to better health outcomes. IR addresses different aspects of implementation including social and contextual factors (poverty, environment, culture), the process of implementation (which approach best answers the implementation issue?) or the outcomes of implementation (clinical/process end points). For example, in case of a new vaccine for prevention of dengue, basic science and traditional clinical research address vaccine development and safety and efficacy testing. IR then addresses the questions of accessibility, acceptability, appropriateness, and feasibility in the communities where the vaccine is needed. IR questions, however, are not always related to a clinical disease entity or implementation of a treatment or prevention program. IR also addresses process issues in health care delivery, as well as cost-effectiveness, policy uptake and implementation, health education etc. IR therefore draws on a wide variety of research approaches to address the diverse research questions. The research designs therefore are not restricted to traditional trial designs, but include methods such as participatory action research (PAR),[1] qualitative design, and effectiveness implementation hybrid designs [2]. Flexibility is a great advantage in IR as the research question largely drives the design, the research process is iterative, and the findings at each stage feed back into the design. IR is usually carried out in close collaboration between researchers and disease control programme staff or policy-makers. The costs are generally modest, yet IR has the potential for a large magnifier effect, as effective implementation expands the impact of health interventions delivered by programmes. As a pre-requisite therefore to the design of a successful implementation strategy, the clinical/public health problem must be identified, the epidemiology of the disease/health status must be understood, and a situation analysis must be performed to identify why access is suboptimal, and what the actual bottlenecks/gaps in care delivery are (not merely presumed), such that interventions can be targeted to reduce these bottlenecks/gaps. In the case of adoption of a successful intervention from one country by another country or scaling-up of interventions from a pilot phase to a wide area, a local situational analysis should be carried out to determine differences and similarities between the communities where an intervention has been successfully implemented and the communities in which the intervention will be tested. IR is relevant when this analysis shows important differences but points to the proposed intervention as the most appropriate strategy, or justifies full scale implementation of the intervention [5]. Awareness of the appropriate application of ethical principles in IR is important in study design and data generation to ensure ethical conduct of IR and to effectively contribute to health system strengthening. In the planning stages, researchers must also be able to effectively communicate their consideration of the ethical principles to research ethics committees, who must also have insight into the adaptations of ethical principles required in IR (as opposed to traditional clinical research) such that protocols are appropriately and fairly reviewed.

Are there ethical considerations which apply particularly to implementation research?

IR is aimed at identifying the best process to implement and scale-up research evidence, whereas biomedical and clinical research focuses on establishing the evidence. This fundamental difference between clinical and implementation research necessitates a modification in the application of ethical principles in their conduct as highlighted in Table 1.

Most researchers and research ethics committees are familiar with the ethical challenges posed by traditional clinical research, which emphasizes respect for individual autonomy and the importance of individual informed

Table 1 Differences between clinical and implementation research which impact application of ethical principles[a]

Domain	Clinical research	Implementation research
Research participants	Individuals	Countries, institutions, communities, and individuals
Informed consent	Informed consent by competent individuals, assent by minors and consent by legally authorized representatives	Consent may be difficult to obtain in cluster randomized trial design. There may be a need for a two level consent—consent for randomization from gatekeepers and consent for participation at the individual level. Sometimes individual consent may not be feasible. However, gatekeeper consent does not replace the need for individual consent. Ethical committee should oversee the informed consent requirement and process
Equipoise	Clinical equipoise	Clinical as well as contextual equipoise (genuine uncertainty that the implementation will work in a new context as well as whether the implementation package will work at all)
Pre-requisites	Understanding of disease pathophysiology Intervention aimed at disease-specific management	Identification of population health needs Understanding relative priority of need for intervention within local context Community engagement to understand community needs, ensure scalability, and sustainability
Research conditions	Generally controlled research environment	Real-life or pragmatic research environment
Research designs	Cross-sectional, case-control studies, Cohort studies, randomized clinical trials	Cluster randomized trials Pragmatic, mixed methods, effectiveness implementation hybrid designs, participatory action research, quasi-experimental design, realist review
Integration within health system	Often, there is no a priori plan for health system integration. Findings of clinical research go through IR before integration into health system	IR has a strong health system strengthening focus. It creates horizontal integration into the health system. There is an ethical imperative for health system integration
Predominant research disciplines	Physiology, genetics, biochemistry, and other basic sciences, epidemiology, clinical medicine	Anthropology Economics Epidemiology Political science Public health Sociology
Control groups	In most epidemiological designs, control groups are required. But some phase 1 clinical trials and observational studies may not require control groups	Having a no intervention control group may not be acceptable. Alternative designs of quasi-experimental studies do not require a control group
Boundary between research and clinical care	This boundary is usually clear, but may be unclear in case of therapeutic misconception especially in cancer trials	Is often unclear, because the intervention is of proven efficacy
Types of research question	Efficacy and safety of a therapeutic strategy in the individual	Operationalization of an intervention in local context Implementation of an intervention in local context prior to scale-up Policy analysis Health system functioning at multiple levels
Anticipated outcomes	Well-defined hypothesis at the beginning of the clinical research. Expected outcomes clearly stated.	Multifaceted holistic impact on health systems functioning with regard to intervention tested. Sometimes outcomes may be unexpected
Risks assumed by:	Mostly, the risks are for the study participants. However, families and communities may also be affected in specific contexts	Usually population level risks. Moreover, the people getting the benefits and people suffering the risks may be different.
Benefits accrued by:	Benefits accrue to the participants, the community. The research finding may be a common good	Individuals, communities, health system, institutions may benefit. The research findings may be common good. The people accruing benefits may be different from those who suffer risks
Generalizability	Generalizability is sometimes possible in multicentric and well sampled studies, however most studies are specific to the target populations.	Generalizability may be limited by contextual factors. However, findings may be generalizable to similar contexts
Social justice implications	Social justice is usually not a primary consideration. However, justice considerations are required in selection of research participants. Research on vulnerable participants is often contentious because of compromised autonomy and other logistics	Social justice considerations are primary. Working with vulnerable groups essential to understand implementation issues in these groups so that the intervention can reach them

[a]Developed from References [2, 6–13, 20, 43]

consent, beneficence, justice, and the necessity for clinical equipoise. Clinical research is usually carried out to answer a focused clinical question, under controlled circumstances, in a well-defined subject cohort with rigid inclusion and exclusion criteria. In IR, in contrast, because the goal is to generate knowledge that leads to wide-scale implementation of interventions in new contexts, the priority focus is different from that of clinical research [2, 6–13]. IR tends to occur in real-world circumstances to test the feasibility and effectiveness of an intervention in real-life situations and not under the controlled environs of clinical research, therefore the boundary between research and clinical care/public health practice can be quite blurred. The implementation ethics issues that arise in the context of IR may also be distinguished from those that arise in the context of programmatic implementation [14]. A priority in IR is broad inclusion of research subjects, specifically including vulnerable populations to optimize equity and justice in access to the intervention. An ultimate goal of IR is to generate knowledge that will be translated into health policy and health action, and therefore studies must be conducted with the vision of sustainable scale-up and roll-out of effective interventions. Although many ethical principles are common to biomedical research and IR, there may be some differences in the way these principles are applied. The key ethical issues relating to IR may be broadly divided into those that arise during the planning phase, the implementation phase, and the post-research phase. Although some ethical issues cut across multiple phases, for the purposes of this review we will discuss the issues as illustrated in Fig. 1. A case study is presented in Table 2 to illustrate the relevance of such ethical issues in the conduct of IR (case adapted from published experiences for the didactic purposes of this manuscript) [15].

Ethical concerns in the planning phase of IR

Responsiveness of IR

Problems addressed by IR must be of high local priority in order to justify the research [16]. One could argue that the requirement for responsiveness is greater from IR compared with clinical research as IR should address priority health needs whereas clinical research is concerned more with proof of principle, and wider application should be tested with subsequent IR. Conversely, when there is an available intervention for an important unmet health need in a community, there is an ethical imperative to conduct IR to try to address the implementation barriers. As such, IR studies are often commissioned by local health authorities. The knowledge of which problems are indeed local priorities relies on epidemiology and health data reporting, which may not always be optimal in resource-challenged environments. Engagement with local health experts and communities is therefore essential in the planning stages of IR to determine whether a health problem is indeed perceived to be a local priority. If a particular problem is not perceived to be a local health priority, the ethics of conducting IR becomes questionable [17].

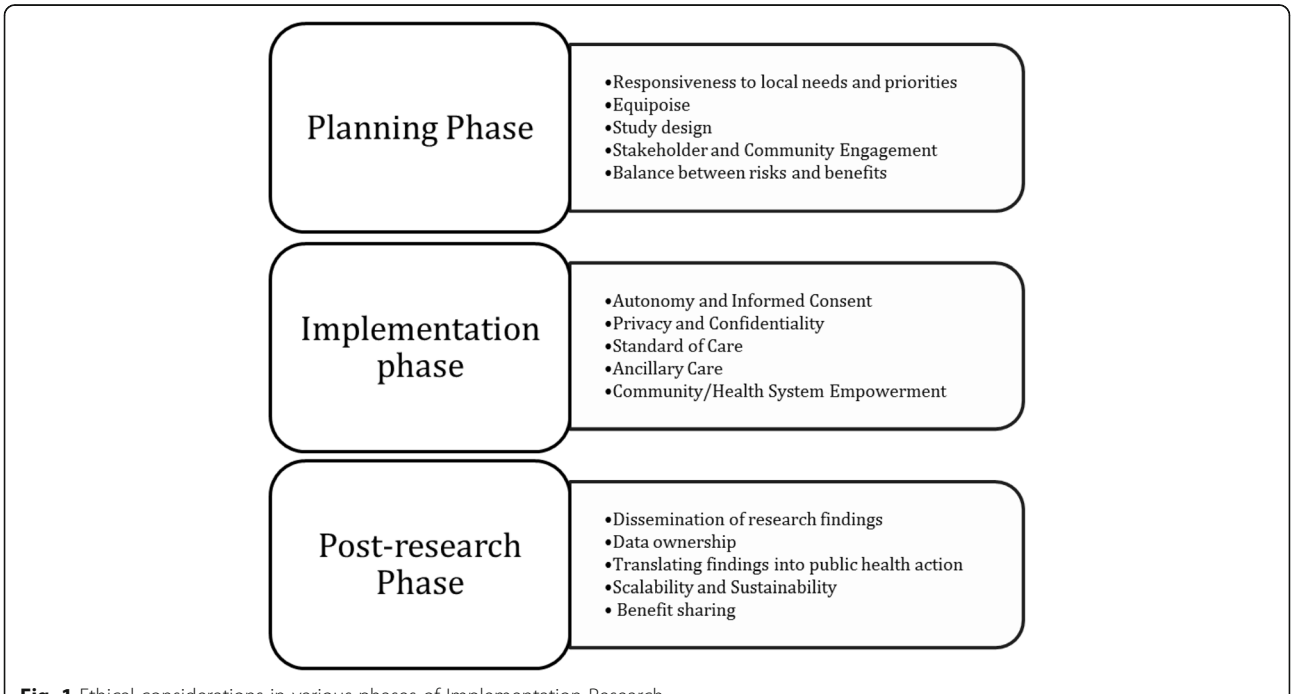

Fig. 1 Ethical considerations in various phases of Implementation Research

Table 2 A case study illustrating the multiple ethical challenges arising in implementation research

Implementation research of strategies to improve vaccine coverage in children in nomadic populations
Study description. Country *X* had a low rate of vaccine coverage largely because a significant group of nomadic populations were not reached by the routine vaccination strategies. A basic needs assessment was performed among the nomadic populations and found their vaccine coverage rate to be very low. In addition, the assessment found that insufficient knowledge of the location of the nomadic populations, lack of logistical support and lack of community engagement in the vaccination drives were important reasons for poor coverage. In order to overcome these problems, an implementation research study was planned. Special Outreach Teams (SOTs) were trained and deployed to a selected sample of known nomadic groups. These SOTs were provided with all logistical requirements such as vehicles, ice boxes, vaccine stocks, and temperature logs. They were also trained to engage with the communities, to deliver the vaccinations to the children under five according to schedule and also to collect data on the existing level of vaccine coverage, numbers vaccinated, documentation of feasibility challenges, and costs. The SOTs coordinated their work with the routine health care workers in the communities where these nomadic groups were stationed at the time of contact. In addition, a small subsample of the nomadic groups were invited to participate in a mobile phone-based GPS tracking study to assess the feasibility and utility of locating the nomadic groups in real-time. Solar powered battery packs were provided to the key members of the community who held the GPS tracking mobile phone. Their GPS coordinates were relayed to the SOTs so that they can deliver their services effectively.
Ethical issues. This implementation research study brings out several important ethical considerations. There is an ethical imperative to engage and work with this special marginalized group in order to increase coverage of vaccination as it is the duty of the health system to protect and promote their health and also in order to more effectively protect the rest of the community with whom the nomadic groups will come in contact. Equipoise to justify the conduct of the study lies primarily in the uncertainty of how the intervention will be taken up and effective within this context as it is known that the vaccinations are effective from other populations. Despite this fact, however, effectiveness of the vaccine should be tracked in this new population as there may be modifiers of the effect, e.g., nutritional status etc. that may also require ancillary care. The findings of the study will help understand the feasibility and acceptability of the intervention among nomadic communities thus facilitating the implementation of the vaccination coverage campaign. Community engagement is a key ethical consideration in this context. Marginalized communities like these have inherent mistrust in health systems and community engagement helps build trust. Identification of appropriate gatekeepers of the community by appropriate selection process will facilitate both the informed consent process as well as representation of long-term voices of the communities. The tracking of the position of the nomadic groups for the sake of facilitating the vaccination process using the GPS tracking system is a significant intrusion into the privacy of the communities. This needs to be carefully weighed and balanced against the benefits of enhanced vaccine coverage and reduced child mortality because of that. Moreover, confidentiality of the GPS tracking data should be clearly maintained. Issues of sharing the GPS tracking position with local health system, other parties who may be interested to track them for other purposes etc. needs to be carefully deliberated. In addition, it is likely that many other health needs would be identified in these communities, raising the ethical issues associated with ancillary care responsibilities.

Equipoise

Equipoise is an important ethical imperative in the conduct of research, it is required to justify any potential risk to research subjects. Clinical equipoise refers to the fact that investigators conducting a randomized controlled trial do not know in advance if an intervention is better than what it is being compared with. In IR, however, such clinical equipoise is generally not present (e.g., a medication is known to cure malaria), but instead, situational or contextual equipoise justifies the conduct of IR, i.e., there remains genuine doubt whether a new and untested package of interventions will work in a specific context [18]. To ethically justify IR, therefore, equipoise regarding the effectiveness of the implementation processes must be preserved.

Study design

A balanced discussion about study design is important before embarking on an IR study to weigh the ethical obligation to ensure scientific standards are maintained against the ethical demands of equity and justice [2, 19]. Though the randomized controlled trial is considered the gold standard in clinical research, health system strengthening interventions often do not lend themselves to such a design. Many different study designs, often with multidisciplinary involvement, have been used in IR, each raising particular ethical concerns [17]. Both qualitative and quantitative methods are used in IR and often within the same study. Examples of specific and different ethical considerations may arise with each method as outlined in Table 3. CRTs are often used in health systems research, but when a public health intervention is known to be effective, withholding the intervention from those randomized to the control arm is ethically problematic [4, 20, 21]. As a compromise, a stepped-wedge approach is sometimes justified to address this dilemma in CRTs, as this may mirror the real-world scale-up process [22]. In a stepped-wedge design, an intervention is delivered sequentially to groups of participants with the goal of ultimately including all participants, however in the early stages some groups do not receive the intervention and therefore are analogous to *controls*, which may pose an ethical challenge even if short-term because for that short period of time the participants are deprived of the proven intervention [23]. Alternatively, quasi-experimental designs where a control group may not be included may be ethically more acceptable in IR, but the scientific rigor and validity may be questioned [24]. The use of random allocation, without consideration of the specific needs and vulnerabilities of the participants, raises concerns of justice and equity. Other appropriate study designs for IR include pragmatic designs, hybrid and mixed methods designs, and open-label demonstration projects which may each have specific ethical issues that will require careful consideration at the planning stage [25–27]. Engagement with all stakeholders is crucial to develop the most effective and fair study design.

Table 3 Ethical issues relating to examples of implementation research designs[a]

IR design	Features	Example	Ethical concerns
Cluster randomized trials (group randomized, place-based, community wide intervention trials)	-Random allocation of groups or "clusters" to study arms and outcomes are measured in individual subjects and at community level	-Randomization of clusters of obstetrics unit staff to education on hand washing or usual practice, measurement of rates of puerperal sepsis in women delivering at study clinics	-Different units of intervention and outcomes measurement -Consent before and after randomization, whom to consent? -Choice of gatekeepers -No opt-out option within cluster -Risk: benefit balance -Ethics of randomization to known intervention, equipoise, -Identification of vulnerable groups
Effectiveness-implementation hybrid trials	-Assess both effectiveness and implementation strategy simultaneously -Identify intervention—implementation interactions	-Evaluate impact of ITN on reduction of malaria and assess robustness of availability and uptake of ITNs in the community	-The trade-off between the scientific rigor required for effectiveness assessment and the realistic contextual considerations required for implementation is an important ethical consideration
Mixed-methods research	-Use of both qualitative and quantitative methods -Understands various perspectives -Rationales: "participant enrichment", "instrument validity", implementation validity", "meaning enhancement"	-Integration of HIV and TB management in single clinics—patient experience (qualitative) and adherence (quantitative)	-The trade-off between the scientific rigor required for quantitative methods and the realistic contextual considerations required for the qualitative component
Participatory action research	-Research question, design, and data collection in a participative manner by the research participants -"Bottom-up" approach	-Peer support groups to improve adherence to ARV in HIV + subjects	-There is a need for community engagement to ensure responsiveness, sustainability, and scalability
Pragmatic trials	-Effects of intervention in routine practice -Maximize variability of settings, practitioners, patients	-Introduction of community health workers for home management of malaria	-There may be concerns of standards of care and ancillary care, which in pragmatic conditions may be ethically debatable.
Quasi-experimental study	-Real-life conditions -With or without control group No randomization	-Open label demonstration project of effectiveness of self-reported use of pre-exposure prophylaxis for HIV	-There is a concern regarding scientific rigor of the research
Realist view	-Analysis of how and why an intervention works in a context combining theory and empirical evidence.	-Integration of traditional healers into home management of malaria strategies	-Community engagement is of utmost importance to retain cultural and contextual sensitivity

[a]Adapted from References [5, 17, 20, 21, 24, 26, 60]

Stakeholder and community engagement

The term *stakeholder* has numerous definitions, many of which are contextual [28]. Two general definitions are relevant in the context of IR: the first defines a stakeholder as a "person or group with an interest, involvement or investment in something" [29]; the second describes stakeholders as "people who will be affected by a project, or who can influence it, but who are not directly involved in doing the work" [30]. Key stakeholders in IR may include the government, policy-makers, public health functionaries, health care providers, health care managers, financing mechanisms, health care industry, and the community. Communities may include individuals on who interventions are planned, the broader community or social structures to which these individuals belong and the broader society to whom an intervention may eventually be rolled out. Communities and individuals with specific roles are important stakeholders in the research process. Meaningful engagement with stakeholders at all levels is crucial in IR, as a means to identify health priorities, to identify key participants, to communicate transparently and effectively about the goals, design, risks, benefits, and process of a proposed intervention, to gain trust and develop partnerships to enhance success of the study, and to gain feedback and identify unforeseen barriers that could be mitigated at the planning stage [31, 32]. Community engagement is a related but different concept where the members of the community who will benefit from or face the risk of the IR are actively consulted and engaged with, with the goal that they play an active partnership role throughout the IR process.

Stakeholder and community engagement are cross-cutting processes which must be carried out during the planning, implementation, and post-research phases of

IR. Particular ethical underpinnings of engagement with policy-makers and health financers at the planning stage include determination that the intervention will address a local priority health need and to gain buy-in and commitment for the scale-up and sustainability of an effective intervention. Scale-up is considered by some to be an ethical corollary of IR. Important ethical goals for engagement with communities as partners in planning and design of IR include to determine acceptability of a proposed intervention, maximize uptake, ensure inclusion of vulnerable populations, establish accountability processes, and particularly when individual informed consent is not feasible due to the research design, to ensure individuals are aware of the rationale and opt-out possibilities. The process of decision-making in IR should consider the power differential between the researchers and the community and allow adequate representation of the research participants and the community at large [33–35].

Often community representatives are selected to facilitate communication between researchers and the community. The selection of community representatives must be an inclusive and fair process of democratic election or nomination, guided by the community itself, to ensure appropriate, acceptable, and comprehensive representation of all sectors of the community irrespective of class, race, gender, sexual orientation, or ethnicity and to avoid any potential conflicts of interest-specific individuals may have [33–36]. Engagement with disadvantaged and marginalized groups is imperative up-front and throughout the IR process to ensure acceptability and equitable participation in IR, and importantly, to identify any specific unanticipated barriers they may face and to develop strategies to mitigate further marginalization or stigmatization through the research [8, 37].

The balance between the risks and benefits

The clinical efficacy and safety of an intervention is generally known before IR is conducted. In clinical research, an individual participant can personally weigh the relative risks and benefits before giving their informed consent, and the risks and benefits are usually borne by the same individual. For example, in clinical research testing, the efficacy of a new vaccine, the benefit of personal protection, and the risk of side-effects are borne by the individuals who participate in the study. In IR, for example in mass drug administration interventions, the community may benefit from large-scale treatment of individuals, but an individual may experience side-effects from a medication they may not personally have required. In addition, the potential risks of an IR intervention may also result from the modality of implementation [2]. For example, a community wide public health screening campaign for sexually transmitted infections which had been successful in one low-income country may carry different risks of stigmatization, religious ostracism, and social discrimination if implemented in an underdeveloped and religiously orthodox country, leading to a different risk-benefit balance. The risks associated with IR may not always be obvious up-front as health systems are complex adaptive systems, and interactions between the components in the health system are not often clearly understood [38]. Diligent situational analysis must therefore be conducted during the planning phase of IR to identify potential risks before harm is done [19]. In addition, a particular feature of IR is that at times an intervention is implemented in one group, but the benefit may accrue to another group [2]. For example, IR studying the implementation and uptake prior to scale-up of a malaria transmission-blocking vaccine exposes vaccinated individuals to the risks of vaccination, but unless a large proportion of the community is vaccinated, the individuals vaccinated will protect others from malaria transmission, but will not be protected themselves. How to balance the risks experienced by one group against the benefits gained by another requires ethical deliberation and effective communication with the research participants. The ethical deliberation should be based on the solidarity principle and should be transparent, involving communities and all stakeholders [39]. To what extent individuals within a group should be exposed to risks for the benefit of others cannot be clearly defined, but it should be decided based on community and stakeholder consultations [2]. A line which cannot be crossed is knowingly exposing one group to harm or significant risk for the benefit of another.

Ethical concerns in the implementation phase of IR

Autonomy and informed consent

A key principle driving the ethics of clinical research in humans is individual autonomy. In public health research autonomy has two dimensions, one concerns individual autonomy and the other concerns relational autonomy in the context of the community to which the individual and the health system belong [40]. Informed consent is the process through which a research participant can exercise their autonomy. In clinical research, a fully informed individual can determine whether or not they wish to freely participate in a study and can usually opt-out of the research at any stage. In IR, there may be difficulties in operationalizing informed consent [2, 20, 41, 42]. For example, an individual in a cluster in a CRT may not have the chance to decide and give consent to randomization as randomization happens at the cluster level. In the case of non-excludable cluster level, interventions such as environmental modifications, an individual may not be able to exercise a meaningful refusal to participate. In such situations in IR therefore there is a need to articulate informed consent differently from traditional individual consent in a

clinical trial. At one end of the spectrum is a complete waiver of individual informed consent where the ethical risks are minimal, and the interventions are largely at a cluster level (i.e., no individual can opt-out), rendering refusal meaningless. For example, in an IR study of an ultraviolet wave system to provide safe drinking water to a population, the harms are considered minimal, and it is not possible for any individual participant in a cluster randomized to the intervention arm to easily opt-out of the study [43]. Such a waiver of consent does not however preclude the need for meaningful community engagement and provision of information. At the other end of the spectrum is the example where individuals have the opportunity to refuse participation in the research project, even though the intervention will occur at the cluster level. This could occur for example when public health professionals wish to test whether community health workers can be trained to provide injections in the community, and individuals have the option to refuse participation and visit the health facility to receive the injection from a nurse. Individual informed consent would be the norm in this case, even though consent for randomization cannot be provided by the individual and it is operationalized at the cluster level prior to individual contact [20, 43]. In the middle of the spectrum is dual consent from gatekeepers and individuals. Community agreement relies on the identification of an appropriate gatekeeper, who should have a keen interest in the welfare of the community and represents the community in a fair manner [36]. There are several challenges in selection of the gatekeeper. In traditional communities where collective decision-making is practiced, selection of a gatekeeper may not be problematic. But in more complex societies, or more complex studies, selection of one voice to represent the community is often challenging. The community leader may not be the most appropriate person to make decisions on whether a community or its members should participate in a study or not. For example, an elderly male village leader may not be an appropriate gatekeeper to consent to an IR intervention on pregnant women in his community. Selecting community representatives fairly requires inclusion of a variety of representative stakeholders, especially those from the target groups, and ensuring transparency of the process [20, 36]. The agreement of the gatekeeper, however, cannot replace individual consent or assent where relevant as discussed above [4]. Ultimately, it is important that proper ethical oversight is in place through Institutional Ethics Committees to ensure that the appropriate informed consent process is followed, maximally respecting autonomy of individuals in the study [44].

Challenges in operationalizing informed consent in the context of IR also include whether the beneficiaries are individuals or populations, and appropriate identification of who the actual research participants are [18]. For example, when implementing a taxi voucher system to increase the rates of institutional deliveries and reduce maternal mortality, should consent be obtained from the pregnant women, the taxi drivers, or the health care workers whose performance will also be evaluated? The Ottawa statement on ethical conduct of cluster randomized controlled trials define a research participant as: the intended recipients of the experimental or control intervention; the direct targets of experimental or control environmental alterations; persons with whom researchers interact to collect their data; persons whose identifiable private information is accessible to the researcher for collection of their data [21]. As such, in the example above, patients and health care workers should provide consent, but whether this should extend to the taxi drivers is questionable and may be difficult to operationalize. A further important ethical issue in the informed consent process is the extent of information to be revealed to the participants in the intervention and control arms, where applicable. In IR, especially when behaviour change interventions are being studied, knowledge of the intervention itself may change the outcomes and implementation process. There is, therefore, often the need to conceal some information about the intervention. The ethical justification for this is debatable, and it must be balanced against the risks/benefits and the potential impact on study validity as discussed in the CIOMS guidelines [45]. The informed consent process in IR therefore may be quite different from that in clinical research and requires thorough consideration to ensure optimal ethical conduct of IR.

Privacy and confidentiality

Particular issues relating to privacy and confidentiality in IR relate to the fact that IR often requires that facility level data on patient outcomes be available or that individual level data from facility health records be obtained. For example, if a public health intervention is implemented to regulate institutional deliveries and improve the quality of skilled institutional deliveries, there may be interventions at the health facility level, but confidentiality restrictions on access to data from women who deliver in the facilities may hamper effectiveness analyses of the health system impact [19]. In such cases, the data that is obtained from facilities should either be anonymized, or the individuals about whom data is being sought should provide consent for their data to be reviewed by the researchers. Where such consent is not possible, it is the responsibility of the researcher to obtain a waiver of consent from the respective ethics board, and put in place mechanisms to ensure that the confidentiality of the patient information is respected. A proactive strategy of informing patients about potential data collection for research and quality improvement

purposes up-front, but reassuring them about privacy and confidentiality could also serve strengthen the patient-researcher partnership and build trust [46].

Standard of care or prevention

There are two approaches to decide on standard of care or prevention to be given to a control group [47–49]. One approach is to allocate the *local de facto* existing standard, which in some situations may be grossly insufficient, making it ethically unacceptable based on justice and fairness principles. For example, in an IR trying to study prevention of mother to child transmission of HIV in a country where routine anti retroviral therapy is not available, the *local de facto* standard of care is no treatment. Having a placebo control arm in the study is not acceptable in spite of the *local de facto* care being no treatment, because an effective treatment which reduces transmission is available and should be accessible to the mothers. The second approach is to provide the *local de jure* standard of care or prevention, which is agreed upon by public health experts of that region and is acceptable to the community. This approach may still be unfair in that this standard may be unsustainable for the local health system after the IR is completed. For example, in a public health behaviour change implementation study focused on hand washing among schoolchildren, the intervention group receives a school-based lunchtime hand washing program, and the control group receives soap and water in all schools, but without any emphasis on hand washing before eating. In this case, the standard of care is provision of hygiene tools, and the intervention is emphasizing the use of these tools. In this context, allowing the control group to have no intervention can be considered ethical. The consideration of standards of care or prevention may therefore identify new gaps as targets for future IR.

Ancillary care

Ancillary care refers to the identification of problems that may contribute to ill-health that are beyond the scope of the study in question, for example, researchers studying home management of malaria may come across household members with other diseases needing attention [11, 50, 51]. Sometimes ancillary care responsibilities can be foreseen at the design stage and at others they are encountered only during the conduct of the IR. Ancillary care obligations are present when the need is serious in terms of severity or urgency or both and when there is a possibility of provision of care within the scope of the research [11]. For example, in the school-based hand washing behaviour change IR study, uninterrupted tap water supply may be lacking and this is an ancillary care requirement. However, this example illustrates that it may not be realistic to expect implementation researchers to assume all ancillary care responsibilities. Researchers may not have the expertise to provide the ancillary care; the provision of the care may be costly or may require system-level interventions. The researchers must, however, establish process of accountability for ancillary care need identified through the research, determine which needs may realistically fall within the scope of responsibility of the researchers, and proactively engage with the local government or non-governmental organizations during the planning and conduct phases of IR to identify who will be able to meet other needs [52].

Research capacity and health system strengthening

Well conducted IR should lead to strengthening of research capacity of the local institutions as well as individuals' capacity to conduct research in settings where such capacity is weak [53]. Research capacity strengthening can range from creating a trained workforce of researchers and research volunteers up to training and capacity building of research experts and infrastructure to permit independent conduct of locally responsive IR in the future. Based on the need in the area where the IR is being conducted, appropriate research capacity strengthening should be facilitated. This can be facilitated by appropriate stakeholder engagement ensuring commitment by donors and governments to build sustainable research capacity. Not only is it important for the IR to strengthen local research capacity, it should also strengthen the health system within which it is conducted. For example, true partnership in an implementation research study of rapid diagnosis of tuberculosis resistance should build sustainable infrastructure in technology required, expertise to run and maintain the technology, strengthen the local health information system to track data acquired, train local researchers in design, conduct, analysis and reporting of study findings as well as participation in post-intervention scale-up, thereby strengthening the local research and health system capacity. IR projects focusing on specific health gaps may, however, create vertical program structures within the health system which may be disempowering to the system through inefficient resource utilization [13]. It is ethically important that the conduct of IR should focus on horizontal integration of public health interventions into the health system such that a project empowering any component of the health system may have positive repercussions for the entire system. Strengthening the capacity to translate research findings into health policy is a specific imperative in IR and must be a component of all phases of the IR process [53].

Ethical concerns in the post-research phase of implementation research

Dissemination of research findings

Given the important public health impact of IR, there is an ethical obligation to disseminate the research findings

widely, including feeding back to the communities and stakeholders who participated in the research [54, 55]. If an implementation strategy had a negative or positive impact in a certain context, either finding may be important for researchers planning similar interventions elsewhere. Therefore, irrespective of the results, the findings of the IR should be disseminated. Furthermore, resource utilization globally could be enhanced by an imperative for dissemination of IR findings, as once an intervention has been tested in many different local contexts, its findings may be presumed to be generalizable and obviate the need for new IR studies and delays in scaling-up of the intervention in new contexts.

Data ownership and sharing

In case of donor or sponsor-driven IR, data is often owned donor, who may regulate and restrict further handling of the data. Data ownership should be fairly negotiated through transparent stakeholder engagement in the planning phase of IR, and ethical oversight of the data ownership process is required to ensure appropriate access to the research findings by the relevant stakeholders post-study, including the local researchers and communities when appropriate, to maximize the utility of the knowledge generated. It may be acceptable for researchers or donors to *own* data without further responsibility. However, given the policy and public health implications of IR and the necessity of trust especially with the communities, there may be a responsibility for data sharing which should also be negotiated up-front, considering the important implications of protecting privacy and confidentiality as well as to allow strengthening of local research capacity.

Translating findings into public health action

Due to the inherent nature of IR, there is an ethical obligation for IR findings to be used to inform effective and equitable public health action. This necessitates timely consideration and uptake as relevant of the IR findings into public health policy and practice. Potential barriers to translating knowledge into action include lack of prior consultation with policy-makers, lack of funding, weak health systems, poor communication of findings by researchers to policy-makers, and absence of a culture of evidence-based decision-making among others [53]. Therefore, in order to translate the research into public health action, implementation researchers should engage with policy-makers and health system officials, important stakeholders in IR, upfront to ensure commitment to sustainability should the intervention prove successful, and must communicate their research findings rapidly, clearly, and concisely to engage and inform policy-makers in a timely fashion. Researchers should also propose actionable suggestions based on the research findings to facilitate uptake and scale-up of successful interventions. Barriers identified during IR may require further study to develop strategies to overcome them. Effective communication between researchers and policy-makers, as well as education of the public are important social justice obligations in IR, ensuring that expectations raised during the research are met, and those who participated as control subjects gain access to interventions withheld from them during the study.

Scalability and sustainability

Scalability and sustainability are important ethical considerations at both planning and post-study phases, as ultimately these are the goals of IR [13, 56]. The duty to ensure sustainability post-study cannot only lie with the researchers. Multiple stakeholders must come together to promote this goal which requires ongoing stakeholder engagement throughout the IR process. The researchers should ensure through effective engagement during the planning and conduct stages of IR that the non-research stakeholders such as policy-makers, local providers, and health system officials remain committed to sustaining implementation of an intervention if found to be effective. If access to a proposed public health intervention cannot be ensured for a community after the IR, it may not be ethical to carry out such a research activity. If specific interventions are provided during IR without a plan for sustainability, this could lead to exacerbation of inequity and harmful effects to the community as well as loss of trust in the health system.

Benefit sharing

Irrespective of the context in which IR is conducted, LMIC or developed countries, there is an ethical obligation to share benefits of the IR with the community [57]. There are various classifications of the benefits that can be achieved as a result of conduct of the IR. The benefits may be direct as a result of the intervention being studied, or indirect and not related to the intervention per se. The benefits may accrue to individual participants or to the community at large. For example, IR may be conducted in communities where the local health system is weak, therefore success of an intervention may result in introduction of a new intervention that was effective in the local context, providing individual benefit. In addition, the IR likely identified and overcame barriers which would have contributed to some strengthening of the local health system that would have a broader impact. IR researchers can facilitate sharing of direct benefits by advocating for sustainable translation of research findings into action, and sharing of indirect benefits through building research capacity and health system strengthening. The unique nature of IR where the

individuals who bear the risks of the IR are not always the ones who enjoy the benefits is a challenge as discussed above. Optimal benefit sharing can be promoted through proper pre-IR planning and ethical conduct. Community and stakeholder engagement plays an important role in achieving benefit sharing as when adequately informed they can advocate for access to proven benefits. Benefit sharing has important social justice implications, and it is the obligation of the researcher to achieve a balance of risks and benefits to both individuals and communities [58, 59].

Conclusion

Putting public health evidence into practice in specific populations requires the generation of knowledge about the feasibility of public health interventions within a specific context, the relative harms and benefits, how an intervention is taken up, whether it reaches the most vulnerable populations, and the logistics of the implementation process. IR aims to generate this knowledge with the goal of enhancing health system performance while upholding fairness and justice in the reach of the intervention to all parts of the community. The ethical principles pertaining to IR are not unique to IR, but may require adaptation in application given the particularities of IR. The stakes of IR are high because of the research contexts within fragile health systems, the large numbers of subjects involved and the reduced ability to predict outcomes and consequences as compared to clinical research [8]. Awareness of the ethical challenges relating to IR is important throughout the planning, implementation, and post-study phases of the research not only to ensure studies are conducted appropriately and that results are maximally useful, but is also important for ethics review committees and institutional review boards to provide appropriate and insightful review of IR projects.

This paper emerged out of the development of the Ethics in Implementation Research Toolkit. Through the consultation process, an important need was identified to clarify the differences in the application of research ethical principles between clinical research and IR, both to guide researchers in planning and conduct of IR and to facilitate review of IR proposals by research ethics committees. As such, this paper complements the Implementation Research Toolkit (http://www.who.int/tdr/publications/topics/ir-toolkit/en/) and the Framework for Operations and Implementation Research in health and Disease Control Programs (http://www.who.int/hiv/pub/operational/or_framework.pdf). It is hoped that this paper will generate discussion in further refining roles and obligations of implementation researchers in low resources settings and in further defining the obligations of policy-makers and funders in committing to long-term sustainability of successful interventions.

Endnotes

[1]PAR is a community-based approach to research that emphasizes community participation in research design, data collection, analysis, and interpretation. PAR tries to understand situations and phenomena by changing them and making observations. The experimentation is grounded in community wisdom and experience.

[2]Effectiveness implementation hybrid designs include simultaneous testing of clinical effectiveness and effectiveness of the method of implementation. It may be of three types: (1) primarily doing an effectiveness study while at the same time gathering data on implementation, (2) primarily doing an implementation study while simultaneously gather data on effectiveness, or (3) dual testing of both effectiveness and implementation strategies.

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Interpretation:

In *paper 5* the ethical challenges faced by patients, families and health care workers are described. These challenges are all rooted in clinical care and can be considered within the context of the 4 basic principles of biomedical ethics[77]. For many patients with limited resources or living in remote areas the possibility to exercise their autonomy is limited. Some ethicists would contend that simply being informed that dialysis exists as a therapeutic option in their situation fulfills respect for a patient's autonomy. Others would argue that when no real choice exists, it is not possible to truly exercise or respect autonomy. Some go as far as to state that it is important not to "mislead people with unrealistic promises of autonomy".[78] As shown in Chapter 1 (Table 3), a significant proportion of patients disappear from hospital after receiving a diagnosis of kidney failure. This is an autonomous act, but the likely associated distress cannot make this morally acceptable. From the clinician's point of view the tension in addition lies between balancing beneficence and maleficence. It would be easiest for clinicians to offer dialysis if available, regardless of the cost, hiding behind the principle of "doing good" at all costs and transferring the decision-making responsibility entirely to the patient. The choice is however not so simple, because the potential harm done to the patient's family in terms of CHE given the almost certain inability of the family to continue to pay (especially in the case of ESKD) makes the short-term potential benefit very hard to justify. As illustrated in Chapter 2, clinicians are therefore caught between having to defend patient health *versus* institutional resources, patient health *versus* family well-being and sometimes the health of one patient *versus* another.

Achievement of justice in these circumstances requires a level of decision-making higher than the bedside. Policy makers must be prepared to venture into the unpopular territory of priority setting and restricting treatment to some patients who might benefit (i.e. rationing). When such decisions are guided by the system, individual physicians and patients/families are protected to some degree from burdensome decisions, despite having to live with their consequences. The implications of 4 potential policy options are outlined within the framework of Marckmann et al. in *Paper 5* (Table 4).[79] The table has been extended to separately analyze a 5th policy option, that of partial government subsidy. This extension is presented here (Table 4 below), including examples with supporting literature of countries where the given policy or approach prevails, and further consideration of the burdens for patients and health care workers.

Table 4: Extended policy options regarding access to dialysis in sub-Saharan Africa

	Expected health benefits - patients	Potential harm and burdens	Impact on autonomy	Impact on equity	Expected efficiency	Country example	Practical issues	Cautions/ compromises	Burdens for patients	Health Care Worker moral distress	Outcome data
Universal coverage of dialysis for AKI and ESKD	Potential for all to benefit	Diversion of funds to kidney disease away from other diseases	Patient autonomy respected	Good for kidney failure patients Kidney disease prevention programs often not in place	Expensive	*Sudan* *Zanzibar* *Malawi*	Reduce dialysis frequency to reduce costs and increase capacity Infrastructure limited -> in effect dialysis may not be available to all (rationing by "dilution")	Reducing dialysis frequency may not be acceptable for all Donations may drive program (not sustainable)	Patients and care-givers may need to move for dialysis, lose jobs, etc. Transport (and medication) costs not covered	Minimized, but lack of infrastructure may impose choices between patients	Survival and quality of life in Sudan acceptable[80,81] Very few patients gain access in Malawi and Zanzibar[82]
Government subsidy for dialysis	Potential for some to benefit	Diversion of funds to kidney disease away from other disease	Patient autonomy respected if they can afford co-payment	Tends to favour those with resources to pay	Expensive	*Cameroon* *Senegal*	Periodic stock outs when companies decline to deliver supplies because of late payments How high or low should a co-payment be?	Dialysis twice a week Reliance on single supplier, corruption	Large out-of-pocket expenses remain (USD 10 – 20 per treatment, medication, transport)	High if patients cannot afford co-payment	Not all patients can afford subsidized cost. Mortality is relatively high in Cameroon despite subsidy.[83] Peritoneal dialysis programme has good outcomes in Senegal.[84]
Universal coverage for AKI only	Saves lives of patients with AKI	Diversion of funds to kidney disease away from other disease	Respected for patients with AKI	ESKD patients not dialyzed	More cost effective that dialysis for ESKD, short term treatment, may not require much infrastructure	*Ghana* – individuals with NHI[85] are eligible for limited dialysis treatments for AKI. *Ethiopia*	Not all patients have NHI Dialysis not available everywhere Should provide palliative care	If AKI does not recover must face withdrawal of dialysis	Out-of-pocket expenses	Minimized for AKI. High for ESKD, withdrawal of dialysis if non-recovery of AKI	Patients requiring more than the provided coverage must pay out-of-pocket in Ghana.[86]

	Expected health benefits - patients	Potential harm and burdens	Impact on autonomy	Impact on equity	Expected efficiency	Country example	Practical issues	Cautions/ compromises	Burdens for patients	Health Care Worker moral distress	Outcome data
State coverage under limited conditions	Benefit for those eligible to receive treatment	Ineligible patients die	Not respected - rationing	May exacerbate inequities especially for poor, vulnerable, sick	Prioritize peritoneal dialysis (cheaper)? Prioritize Transplant (most cost-effective)?	*South Africa*	Patient selection process may impose delays Should provide palliative care services	Need clear transparent guidelines, community engagement, appeal possibilities	Anxiety, distress, fear, helplessness, lack of understanding	High, but greater moral burden lies with state	Only 25% of ESKD patients are accepted onto the dialysis program in Western Cape, South Africa.[87]
No state coverage	Limited to rich few	Inadequate informed consent will lead to catastrophic expenditure and death	Restricted to rich	Exacerbates inequity	Left to market forces	*Nigeria* *DRC* *Burundi*	Generally only in large cities, very expensive Should provide palliative care services	Lack of government regulation frequent	If not fully informed poor patients may not realize life-long expenditure required	Conflict between profit, doing good, doing harm	Most ESKD patients could not continue dialysis beyond 2 weeks in Nigeria.[43]

CHE – catastrophic health expenditure; DRC – Democratic Republic of Congo; NHI – national health insurance

A widely accepted approach to policy making with the goal of achieving distributive justice is the "Accountability for Reasonableness" (A4R) framework.[88] The A4R framework comprises 4 necessary conditions: publicity; relevance; revision and appeals; regulative, such that decision making is fair, transparent, implementable and open to being revisited. As discussed in *Paper 5*, this approach was used by Moosa et al.[87] to develop transparent and more equitable guidelines regarding access to dialysis and transplantation for patients with ESKD in the public sector in the Western Cape, South Africa. This process was driven by clinicians struggling to decide fairly which patients should gain access to limited dialysis slots. Such processes must include all stakeholders in the quest to maximize equitable access to care within resource restraints and to optimize use of the available resources. As shown in the Western Cape, ongoing monitoring of the outcomes of policy implementation is required: some components of equity have been improved under the new guidelines (more women have access to dialysis), but few patients overall have access to life-saving care, still very dependent on a patient's socio-economic status.[89,90]

Responsible policy making and priority setting should involve iterative cycles of informed planning, implementation and evaluation to ensure goals are being met and undue harm does not accrue. Such a process requires establishment of partnerships across multiple sectors, including civil society, analogous to the optimal conduct of IR.[91-93] Indeed, the goal of IR is to address the needs of the disadvantaged in sustainable and scalable ways. Priority setting is inherently a "value-laden" process, and cannot be whittled down to technical considerations of clinical or cost-effectiveness alone, therefore diverse frameworks are increasingly being used simultaneously.[94,95] Evidence is needed to feed into the deliberative process but interpretation of the evidence requires a broad perspective and consideration of multiple values, with a willingness to learn and adapt such that decision making can be optimized in an iterative fashion.[96] As such, the ethical considerations relevant to the various phases of IR (Figure 1, *Paper 6*) could provide a useful complement to the A4R process for public health policy-making regarding high cost interventions such as RRT. Some authors have suggested the addition of a 5th criterion to the A4R framework: empowerment.[97] Indeed, advancing empowerment and capacity building for patients, communities and those functioning within the health system would conceivably significantly strengthen the policy-making and implementation processes. A

preliminary analysis of the potential relevance of these considerations to policy making regarding dialysis is outlined in Table 5.

Table 5. Ethical considerations as a complement to the A4R priority setting framework regarding dialysis

Phase	Ethical consideration	A4R condition fulfilled	Relevance
Planning	***Responsiveness to local needs***	Relevance	• Reliable data on local burden of kidney disease relative to other conditions • Awareness of ongoing dialysis activities • Priority setting
	Program design	Publicity	• Sustainability? • Location? • Will a form of rationing be required? • Embed in holistic NCD/kidney disease (prevention/early treatment) programme, supportive care for those ineligible for RRT • Consider coverage level (partial, full, none) • Address needs of vulnerable populations?
	Stakeholder and community engagement	Publicity Empowerment	• Patients and communities • Health care workers (public and private) • Health system administrators • Industry – pharma, dialysis • Health insurance industry • Finance, trade, other ministries • Donors, non-governmental organizations • Identify potential conflicts of interest
	Balance risks and benefits	Relevance Publicity	• Opportunity costs • Consideration of those "abandoned" if ineligible • Moral distress of health care workers • Quality standards • Corruption
Implementation	***Respect for autonomy***	Publicity Empowerment	• Community and health worker engagement during policy making process • Transparency
	Standard of care	Relevance Regulative	• Appropriately trained health care workers • Sustainable services • Regulate standards and operation of dialysis
	Ancillary care	Relevance	• Consider impact of out-of-pocket payments for medications, transportation
	Community and Health system empowerment	Publicity Revision and appeals Empowerment	• Strengthen health system at all levels • Openness to feedback and appeals • Promote prevention and awareness of kidney disease
Post-implementation	***Monitoring and surveillance***	Regulative	• Access to care, including vulnerable populations

Phase	Ethical consideration	A4R condition fulfilled	Relevance
	Quality assurance and iterative improvement	Regulative Revision and appeals	• Moral distress • Catastrophic health expenditure • Dialysis service functioning, efficiency, costs • Incidence and prevalence rates • Dialysis outcomes • Monitor opportunity cost implications
	Disseminate findings	Publicity Empowerment	• Dialysis registry • Share experiences

Rigorous evaluation of the process is key, as suggested by the comprehensive framework for evaluation of successful priority setting in LMIC put forward by Kapiriri and Martin.[98] It is also key that more outcomes of actual priority setting processes on policy development and implementation are published to expand the literature and knowledge beyond that of pure research activities.[95]

DISCUSSION

The data generated throughout this PhD serves to fill gaps in prior knowledge relating to the diverse facets of the burden of kidney disease in SSA and the associated ethical implications, and progressively builds the case for the need for pragmatic and transparent policy development in SSA and other low resource settings regarding provision of dialysis within the contexts of the broader health system and the economy.

Although the numerical burdens of AKI, CKD and ESKD in SSA still remain unknown, progress in the GBD study promises to address this in the coming iterations. Regardless of the total numbers, as highlighted by *Papers 1 and 2*, existing capacities to diagnose and manage AKI and ESKD are significantly limited and are inequitably distributed.[65,66] As such, patients present very late, out-of-pocket costs remain unaffordable, and mortality and rates of "disappearance" from hospital remain high. These circumstances raise important ethical challenges across the spectrum of the health system. Reliance on out-of-pocket payments and availability of dialysis services in large urban areas take this therapy out of reach of most patients. As such, among those who try to pay, catastrophic consequences almost certainly accrue, with the patient more often than not dying because care cannot continue and with families having been plunged into further poverty. For physicians, as illustrated in *Presentation 1*, moral distress is frequent as they (and other health care workers) struggle between trying to respect patient autonomy and balancing the spectrum of benefits and harms related to dialysis care for patients, families and institutions. Decision makers face multiple ethical dilemmas in terms of resource allocation, priority setting and transparency. As highlighted in *Papers 3 and 4*, many social determinants of health affect the risk of kidney disease, and some simple public health measures could be effective in reducing the burdens of AKI and CKD, simultaneously with that of other infectious and non-communicable diseases.[10,11] Such strategies however require robust health systems, reliable health information, well trained and well equipped health care workers, and appropriate financing to be in place. Health is also not the only sector requiring attention, therefore policy makers must also prioritize across sectors. Ultimately, as highlighted in *Paper 4*, achievement of the SDGs would potentially go a long way towards reducing the global burden of kidney disease.[11] It is however unlikely that lower-resource countries can achieve these goals

alone. In the spirit of solidarity, the international community (including donors) should engage proactively and allocate more resources to global prevention and to tackle NCDs.[99] In *Paper 5*, the ethical challenges faced by patients, families and health care workers are highlighted to demonstrate the need for policy development and transparency regarding dialysis care in lower income settings, specifically in SSA.[100] It is clear that in most countries dialysis cannot be universally provided by the state, and that the current reality reflects very limited and inequitable access to care. As such, the implications of several potential broad policy options are discussed within the public health ethics frameworks of Marckmann et al. and A4R.[79] The development of policies regarding provision of, and access to, dialysis requires diligent and systematic multi-stakeholder consultation and broad consideration of the implications from all sides. As such, ethical considerations are outlined in Paper 6 to guide the comprehensiveness of this process.[101]

Consideration of aggregate population health does not help the clinician and the patient at the bedside when faced with a choice which would impose CHE. Opportunity costs are however highly relevant especially in low-resource settings. Pragmatic solutions to meet the need for high-cost care in low resource settings are not obvious and therefore should be arrived at systematically, transparently and progressively. Building on the arguments presented thus far, important components of this process include acknowledging the impact of the status quo and the need for priority setting. Priority setting may include the need to withhold or ration expensive care. Each of these in turn will be discussed with reference to dialysis in SSA.

Acknowledging the impact of the status quo in sub-Saharan Africa

If the cost of a month's supply of one cardiovascular medication in LMICs can induce CHE[102], it is not hard to imagine that dialysis, costing many fold more, would always induce CHE if not covered under UHC. According to the recent Global Kidney Health Atlas, chronic dialysis was "available" in 100% of 124 countries surveyed in 2016.[51] As such, various countries have either explicitly, or *de facto*, adopted a form of dialysis distribution and financing as illustrated in Chapter 4, Table 4. Unsubsidized costs for one session of HD across SSA range from USD 100 to 350 per treatment and are only sustainably feasible for a few privileged individuals with their own resources or more commonly through external funders such as religious organizations,

employers or philanthropists.[7,65,103,104] In Cameroon for example, dialysis is largely subsidized by the state, requiring an out-of-pocket payment of USD 10 per treatment. With the minimum wage of USD 50 per month, even this reduced cost is unsustainable for many patients.[83] Countries like Nigeria and Ghana provide access to a limited number of sessions of dialysis for AKI to members of the national health insurance.[85,86] This strategy likely does save some lives, but is inequitable in that only a minority of the population can afford insurance premiums, and this does not address the needs of those whose kidney function may not recover. Some countries only provide coverage or services for adults and not children who need dialysis.[86] Other countries such as Malawi have decided to provide dialysis free at the point of care to a very small number of patients (under 50 in the country), at a per capita health care expenditure of several hundred times that spent for the general population, without any selection criteria in place, and without parallel development of prevention programs.[48,82] A few countries only support temporary dialysis for those who have available living donors and can be sent for transplantation elsewhere (given longer term cost-effectiveness), meaning that patients without a donor do not receive dialysis.[100] "Availability" of an intervention therefore does not mean equity of access, and many patients in SSA die untreated daily because of high costs, geographic inaccessibility of appropriate care, young age or female gender.[1,65,66,105-107] The inherent inequities across SSA, both within and between countries, are therefore stark and remain unaddressed. These circumstances create moral distress for families and health care workers on a regular basis.[108,109]

Provision of dialysis under UHC would seem an obvious equitable solution and is functioning in most high and some middle-income countries.[33] Indeed, for ESKD especially, in *Paper 2* we found that among prevalent dialysis patients in SSA, i.e. those who manage to sustain dialysis for a prolonged period, survival was far superior than among incident patients who often could only pay for a few treatments and had to stop.[65] Sustainable financing is therefore part of the solution. Of concern, however, in South Africa a poor socioeconomic status has been found to be a negative predictor of outcomes in ESKD even when RRT is paid for by the state, and is therefore included, although controversially, as a potential exclusion factor for chronic dialysis.[87,110,111] Similarly, in Andhra Pradesh (India) and at the Sindh Institute of Urology and Transplantation (Pakistan), where dialysis itself is provided free of charge to the patients, 63.5% and 18% respectively of those who initiate dialysis stop treatment within months, most likely

because of uncovered expenses of medication, transport, lodging and lack of family support.[112,113] Payment for dialysis alone therefore is not enough. In addition, if patients die early, the opportunity costs of such expense to the health system does not seem justifiable. In depth objective analysis of what is required in each setting for a patient on dialysis to thrive (including health system components and patient factors) must be conducted in order to understand the true costs and true value of dialysis provision in low resource settings, and to understand how progress can be made. The role of social workers in these contexts is critical.

Priority setting

Priority setting is a cornerstone of health system stewardship. Priority setting dilemmas arise when tradeoffs must be made about what kind of services should be provided and to whom, i.e. a "trade-off" decision to withhold some services from people that could benefit, and to allocate the resources to other services that benefit other people instead.[114,115] For example, in SSA, where resources are particularly scarce and the burden of kidney disease is arguably high, there is an urgent need for relevant evidence to inform legitimate and transparent priority setting and decision making regarding provision of, and access to, dialysis within the contexts of kidney disease as a whole, as well as other health priorities. Some authors suggest that "upstream" public health interventions (i.e. prevention of disease), as maximizers of health and capabilities for the greatest numbers, may be ethically superior and should be prioritized over individual-level interventions.[116] Although likely true, regardless of prevention activities some individuals will develop illness through no fault of their own, and/or possibly because of adverse structural factors tolerated by the state, therefore this illness cannot be ignored. A balance therefore between prevention (i.e. horizontal equity, treating like cases with like interventions) and treatment (i.e. vertical equity, treating unlike cases with unlike interventions) must be struck.

UHC is increasingly being recognized as the fulcrum of an effective health system and it is intricately linked to priority setting. The goal of UHC is to ensure access to priority health services for all at affordable cost, thereby alleviating poverty and advancing equity.[117] The 3 dimensions of UHC include expansion of priority services, reaching more people, and reducing out-of-pocket payments.[117,118] The initial challenge in determining what should be included under UHC lies in determining which essential services are needed and deliverable within a

specific country and budget, with the result that less essential services must be paid for out-of-pocket. The definition of what is "essential" can be debated, therefore this process should not be static, and over time additional services should be progressively included. Priority-setting decisions must therefore consider disease burden, the effectiveness of a relevant intervention and the financial burden imposed by the intervention (covered or not) on the individual and the health system.[117]

The priority setting process therefore requires reliable local evidence on disease burdens. Evidence on cost-effectiveness is important and can be used to rank interventions according to which one would maximize population health gains for a given cost.[119] Despite the seeming objectivity of cost-effectiveness analysis, this is a highly value-laden process in itself, and mounting criticism points out that crucial factors such as financial risk protection for individuals, or equitable distribution of needed interventions, are not taken into account.[120] As such, extended cost-effectiveness analysis, equity impact analysis, equity trade-off analysis, and multi-criteria decision analysis have been proposed in an attempt to include these variables, and are reviewed in detail elsewhere.[121-123] Data from such analyses should be utilized to develop equitable health benefit packages to be included under UHC, however a recent systematic review failed to find a major impact of these frameworks on policy development yet.[95]

Until recently priority has mostly been given to infectious diseases and maternal health, as these are most amenable to short-term interventions, and indeed, are frequent causes death and of medical impoverishment in low income settings.[124] However, NCDs are now the leading causes of death globally.[19] Many NCD deaths can be delayed or prevented with access to basic primary health care and cheap medications, which are currently also frequent causes of CHE in LMICs.[125] Prevention of NCDs also promises to foster economic growth and is therefore cost-effective.[126] Progressively, therefore, NCD prevention, diagnosis and treatment must be included under UHC.

Priority setting and dialysis

An oft quoted "success" story regarding priority setting is that of Thailand, a low-middle income country at the time. UHC was rolled out in 2002 and initially excluded dialysis because of cost.[41] After careful study and broad stakeholder consultation however, UHC was extended to include dialysis in 2008 as it was recognized that dialysis was a significant cause of CHE.[127] Financial risk

protection was therefore the driving force which motivated coverage for ESKD care. To keep costs down, PD was strongly favored and procurement costs were negotiated up front.[41] Service delivery was optimized through capacity building of the health care workforce and quality was monitored through a dialysis registry. Subsequent evaluation of the impact of this policy showed improved dialysis outcomes and a reduction in poverty by reducing associated CHE, but there was also an unanticipated increase in demand for dialysis.[41,117]

How to reconcile state provision of such high-cost therapies in low and low-middle income countries where existing coverage for treatment of high priority common infections like diarrhea and pneumonia remains suboptimal remains a dilemma.[128-130] A policy decision not to provide dialysis until all cases of diarrhea and pneumonia have access to appropriate care could be defended. Would this however mean that the life of someone with diarrhea is more valuable than that of someone with ESKD? Or that someone with diarrhea has a greater right to health care than someone with kidney disease? Policy makers are therefore faced with the very difficult task of simultaneously achieving UHC, setting priorities and fulfilling the human right to health.[131]

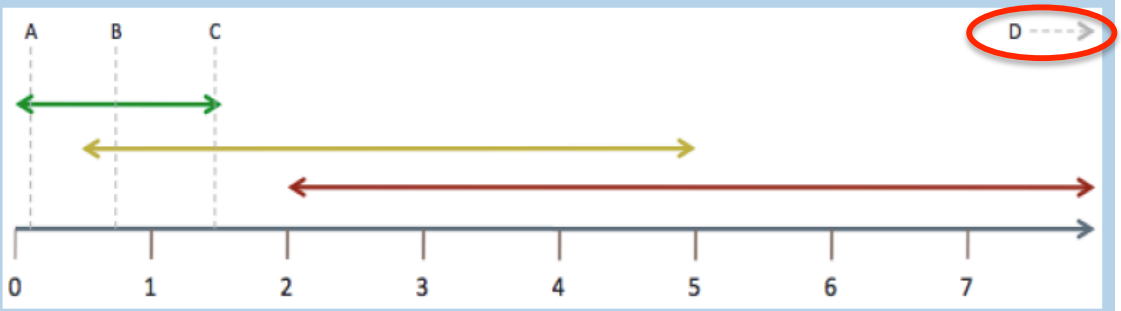
An additional layer of complexity often present in low income settings is that high cost care is (only) available through private providers, religious organizations and non-governmental organizations, which sets up a parallel system where the authorities may not have much oversight over services provided, costs, quality and access. Patients may be attracted by shorter waiting times and a belief of better medicine.[132,133] CHE is likely frequent as a consequence, but if private care is the only care available, patients may essentially have no choice. The private sector is therefore an important stakeholder in public health. Public-private partnerships are being increasingly suggested as the way forward for dialysis financing. Governments must begin to tackle inequity and other challenges posed by the private sector.[133]

To facilitate progress towards UHC, the World Health Organization's (WHO) guide "Making fair choices on the path to universal health coverage"[117] suggests which "trade-offs" are acceptable or not acceptable, e.g. between health maximization and financial risk protection, for fair and equitable health resource allocation. Relative cost-effectiveness is expressed as a percent of gross domestic product (GDP) per capita. Kenya is presented as an example (Figure 6) where

UHC for diagnosis and management of tuberculosis (A) and traffic safety regulation (B) are considered cost-effective "best buys", i.e. saving the most lives at lowest cost, and are therefore considered high priority services, whereas treatment of mild asthma (C), given higher cost for fewer lives saved, would be of medium priority. According to this reasoning, coverage for dialysis (D), despite the significant financial protection it would afford to affected individuals, is deemed too costly, as 300 fewer healthy life years would be saved by dialysis compared to tuberculosis control for the same cost, making dialysis a low priority.[117] The document suggests that only once all high priority services are progressively covered should medium and ultimately lower priority services be covered. As such, dialysis for AKI and palliative care, both highly relevant for patients with kidney failure, are included in the document as worth considering once countries progress towards more comprehensive UHC.[117].

Figure 5. Priority setting framework suggested by WHO Making Fair Choices

The practical use of the framework can be illustrated by applying it to hypothetical cases in Kenya. Using regional cost-effectiveness data and national income data, four services (A, B, C, D) have been placed on the scale.*



Cost per healthy life year as a multiple of GDP per capita

TB diagnosis and Treatment (A)	Traffic Safety Regulation (B)	Treatment for mild Asthma (C)	Dialysis for renal failure (D)
0.1 x GDP per capita per healthy life year	**0.8 x** GDP per capita per healthy life year	**1.5 x** GDP per capita per healthy life year	**> 30 times** GDP per capita per healthy life year

*cost effective = ≤ 1.5 GDP per capita (limits A to C). Reproduced with permission from[117]

Despite this analysis, the Kenyan government recently deployed dialysis machines to all counties in the country after having determined that kidney disease was the most common cause of death in hospitals, that centralized services were overwhelmed and that the out-of-pocket costs for patients were unaffordable.[134] The implications in terms of costs and opportunity costs of

dialysis provision under UHC in Kenya, as well as quality and sustainability, will require ongoing monitoring and evaluation.[135,136]

As shown by both Thailand and Kenya, primary drivers for LMICs to provide high-cost therapies, otherwise considered "unacceptable" trade-offs, are the immediacy of saving lives and provision of financial risk protection. Decisions may also at times be driven by directed donations or other donor or political agendas, which add further layers of ethical complexity especially when these are not aligned with priority health care needs.[98,137] Some have argued that it may be unethical to refuse donations, however the quality and motivation of the donations may be questionable, and the externalities and opportunity costs of creating a program in response to donations may be very high.[138] There are therefore often competing values (technical, socio-political and ethical) that must be juggled in making policy and setting priorities.[64,139-141] The tensions between these values are well illustrated by kidney disease and dialysis as outlined in Table 6.

Table 6. Factors relevant to priority setting regarding coverage of dialysis within the pillars of universal health coverage in SSA

Factor	Considerations	Implications
Disease burden	• Kidney disease is common – incidence, prevalence, mortality	• Requires equitable access diagnosis, awareness of disease currently not present in many SSA countries • Mortality rates from AKI and ESKD are likely high • Requires knowledge of other relative disease burdens
Cost-effectiveness	• Maximize efficiency • Include more people • Opportunity costs	• Dialysis would rarely be considered cost-effective • Opportunity cost for dialysis may be too high • Would favor treating AKI only and not ESKD • Would favor transplantation over dialysis • May favor PD over HD in certain settings • AKI and ESKD affect economically active population, impact on economy unknown
Financial risk protection	• Protect families from CHE	• Coverage of dialysis only does not protect from other expenses, medication, work time lost, travel, lodging etc. • Where UHC cannot realistically provide universal access to dialysis, "rationing" of dialysis could be argued as protecting families from CHE by preventing access to unaffordable dialysis
Favoring worst off ("rule of rescue")	• Renal failure often means imminent death without dialysis • Societal belief that life has value	• May divert resources to dialysis at expense of less "urgent" cases who could benefit more over the longer term • May divert resources from screening and primary and secondary prevention of kidney disease

CHE – catastrophic health expenditure

Broader frameworks for decision making have also been proposed by leading thinkers in the field, such as the Guidance on Priority Setting in Health Care (GPS-Health), incorporating the concepts of cost effectiveness, disease severity, capacity to benefit as well as human rights.[131,142] Whichever framework a government decides to use, the policy making process should be transparent, participatory and relevant in terms of clinical effectiveness, cost and equitable distribution of interventions.[140] Governments should be held accountable for such policies. Importantly, however, communities and health care workers must be effectively engaged with and empowered in the process, and cannot remain passive recipients and deliverers of health care, but must also be active participants in optimization of health and disease prevention and be responsible stewards of allocated resources.

Rationing

In all countries it is difficult to justify provision of dialysis because the cost-effectiveness argument against it is strong. Arguments about protecting patients and families from financial risk protection and favoring the worst off become the deciding factors. As discussed above, in high-income settings the high costs of RRT have been accepted by society as a trade-off for the "well being" of knowing that the severely ill are not being abandoned.[52] This paradigm of the "pricelessness of human life"[52] is however questioned by some especially where the marginal benefit may be small, e.g. dialysis for the very elderly, and has set difficult precedents regarding expensive coverage for other diseases. Although opportunity costs exist in these circumstances these do not yet seem to have reached existential enough limits to have become tangible. It is possible, however, that in the coming years even in high-income countries, rationing may need to be considered.[53,143]

In fact, even though the word "rationing" has negative connotations and tends to be avoided, *de facto* rationing occurs in all health systems, most often by denial (high cost therapy), selection (most likely to benefit), dilution (fewer staff per patient), delay (wait times), deterrence (red tape) and deflection (referrals elsewhere).[53,144,145] Some of these forms of rationing may be justifiable, especially when faced with scare resources, such as allocation of organs for transplantation to those most likely to benefit, but others often exacerbate existing inequities,

such as disadvantaged populations having to navigate complex bureaucracy to gain access to care.

At present in low-income settings it would be naive to insist that dialysis be provided for all under UHC, however dialysis is available and the associated ethical dilemmas cannot be ignored. When policy decisions were made to provide dialysis in lower income settings, for AKI, ESKD or both, this has not often been accompanied by "up stream" guidance in terms of who should have access. As such there is lack of transparency and lack of accountability which are necessary for the legitimacy of the policy process.[140] In most cases, if access to dialysis is not universal, this is often determined in practice by a patient's resourcefulness or on a first-come first-served basis. As discussed above, existing circumstances in SSA cause significant moral distress to both patients and health care workers.

Physicians and health care workers can play diverse roles as rationers, which impacts their relationship with their patients, their institution and may even have political consequences.[146,147] In the *traditional fiduciary view* of bedside rationing, the role of the physician is to advocate for and try to meet the needs and goals of individual patients.[146] This view however disregards the potential impact of individual decisions on society, especially under resource limitations. In the *dichotomized view* physicians should implement rationing decisions made by administrators but continue to advocate as best they can within the set limits.[146] This view does "insulate" the physician from making rationing decisions *per se*, but implementation would require the development of evidence-based guidelines to justify where rationing would be acceptable and would require close oversight.[146] This view would be inconsistent with the Western Cape guidelines developed by nephrologists attempting to advocate for equity among individual patients while functioning within strict limits, but as discussed above nephrologists are not unanimous in their support for these guidelines and therefore practice is still somewhat inconsistent. In the *combined view*, the physician must balance patient advocacy with stewardship of resources.[146] This view would support the development of transparent ethical guidance, developed and accepted through a multi-stakeholder process, where physicians in individual cases would have to weigh relative benefits and harms to the patient and to society in making decisions. Such a system is challenging given the lack of concrete guidance, would be open to a lot of questioning and would be difficult to monitor. How best to negotiate between

these perspectives is unclear and would require more research to understand the implications of rationing on doctor-patient relationships, education of the public and health care workers about the need for rationing, and meaningful engagement with all stakeholders to develop acceptable, transparent and fair processes.[146]

As outlined in Table 7, there are many forms of rationing that have been proposed, each with a potentially acceptable ethical justification (indicated in parentheses).[148] Many of these approaches are however mutually exclusive which illustrates the tensions between them. It is likely when decisions are made *ad hoc*, in the absence of formal guidance, different forms of rationing may be employed at different times leading to unacceptable inconsistency based on implicit or explicit biases of individuals. It is important to bear in mind that "in a resource-constrained system, giving additional weight to something or someone implies that something or someone will lose out"[142]. Given these consequences, fairness and equity must be actively pursued. Responsibility for such existential level decision-making should not be deflected to individual physicians at the bedside, but should be based on transparent nationally developed and accepted criteria.[53,149]

Table 7: Potential dialysis allocation or rationing strategies

Strategy	Benefit	Harm
Ability to pay (Libertarianism)	• Self-selection of candidates • Chance of sustainability	• Highly inequitable, favors those with resources over others
Random chance (Egalitarianism)	• Impartial, all treated equally (lottery, luck) • Physician and patients do not decide	• May not address the needs of the sickest, youngest etc. • Cannot operate when no empty slots are available
Treat first-come first-served (Egalitarianism)	• Physicians and patients do not decide	• May not address the needs of the sickest, youngest • Those with resources to get to a dialysis center have an advantage (tend to be bread-winner men in LMIC)
Give priority to the sickest (Prioritarianism)	• "Rule of rescue" • Addresses needs of the sickest who may benefit	• Requires accurate determination of relative prognosis • Some may be too sick to benefit
Give priority to the youngest (Prioritarianism)	• Gives chance to those who have most life years to gain	• Discriminates against older possibly more productive individuals • Young age on dialysis does not mean long survival, ideally need transplant available for maximal benefit
Maximize lives saved (Utilitarianism)	• Maximizes efficiency • Focus on treating the most "salvageable" – would favour treating AKI over ESKD • Favours transplantation over dialysis for ESKD	• Discriminate against those with comorbidities, other terminal illness • Discriminate against ESKD in favour of AKI • Discriminate against ESKD patients without living donors or ineligible for transplantation
Treat those who would benefit most (Utilitarianism)	• Maximizes efficiency • Focus on treating the most "salvageable"	• Triage cases and treat the "healthiest" • When a new patient would benefit more than an existing patient, creates a dilemma of whether to remove existing patient from dialysis if no empty slots?
Treat those who are more useful to society (Utilitarianism)	• Efficiency beyond dialysis • Favours breadwinners, parents, employed i.e. "social worth"	• How to weight "usefulness" • Discriminate against very young, elderly, those with co-morbidities • Recreates "God Committee" from USA in 1960s/1970s
Reciprocity (Personalism)	• Favours those who contributed in the past (e.g. a kidney donor who may develop ESRD may have priority for dialysis)	• Discriminates against those who have not had a prior opportunity to contribute
Redressing inequalities (Personalism)	• Minimize differences between population groups	• Discriminates against groups that historically may have done wrong, but present members (e.g. children) may not have participated in wrong-doing (e.g. apartheid)

Strategy	Benefit	Harm
"Complete lives system" (Prioritarianism)	• Favours adolescents and young adults • Focus on "lives' rather than "experience" • Favours those with better prognosis • Uses lottery to decide among equal candidates	• Discriminates against very young and older • Discriminate against those with more comorbidities
Non-abandonment (Egalitarianism)	• Tries to allocate limited resources fairly/proportionately across all high cost chronic diseases within a limited budget • Rationing fairly	• Not all individuals gain access to care
Ensuring an acceptable minimum standard for all (Sufficientarianism)	• Improve health of all up to a minimum level	• Favors provision of primary care and prevention, early diagnosis treatment under UHC for kidney disease • Under resource limitations - unlikely to justify state provision of dialysis until the minimum "sufficient" baseline is met for all first • Does not consider inequities above the minimum threshold to be unjust e.g. provision based on ability to pay • May justify reducing "quality" in order to increase numbers of patients that can be dialyzed (e.g. providing HD twice instead of 3 times a week)

Table extrapolated from concepts summarized by Persad et al.[114] and others[140,144,148,150-153]

Rationing in practice is complex

Taking South Africa as an example, dialysis for AKI is generally accessible, but dialysis for ESKD is rationed in the public system, which caters to 84% of the population.[110] In the Western Cape, guidelines have been developed using the A4R framework as discussed above and in *Paper 5*, where patients are accepted for chronic dialysis only if they are considered "transplantable".[87] Kidney transplantation is more cost-effective than dialysis. The ability to provide transplantation in South Africa has simplified the rationing process to some degree, in contrast to the multiple options outlined in Table 7, in that a relatively clear objective ("transplantability", i.e. a utilitarian approach was taken to allocate resources to those most likely to benefit most) is articulated. The guidelines outline 3 patient groups based on inclusion and exclusion criteria: Category 1 (< 50 years, otherwise healthy) - unequivocal acceptance; Category 2 (50 -60 years, or generally clinically acceptable but poor social circumstances, prior conviction of an offence etc.) – accepted if resources permit; Category 3 (> 60 years, medically ineligible for transplantation) – dialysis declined. Although "transplantability" is accepted as the overarching criterion in the public sector in South Africa, these guidelines have not been formally adopted by the rest of country largely because some nephrologists are not comfortable with denying access purely on the basis of socio-economic criteria considered a "grey area" in Category 2.[110] In reality, given the low rate of organ donation, patients remain on dialysis for prolonged periods and available slots for new patients are very limited adding a further layer of complexity.[110] How children with ESKD fit into this algorithm is not stated. Often children are denied dialysis and transplantation in SSA because of lack of social support.[109] For patients, the waiting period between diagnosis of ESKD and final decisions about acceptance or not is highly distressing, a real sword of Damocles that for most falls.[154]

Dialysis in the private health sector (accessible to the 16% of the population who have private insurance) in South Africa is thriving, with no eligibility criteria for dialysis besides ability to pay.[155] As such, in 2016 there were almost 8 times as many dialysis units in the private compared with the public sector (230 vs. 30) and the respective treatment rates are almost 12 fold different (797.5 vs. 67.5 pmp).[156] Since 1994, there has been no growth in the public dialysis capacity relative to population growth in the public sector whereas the private sector has seen an almost 4000% increase, concentrated in larger urban areas.[155] Some authors have been bold enough to state that in the current South African environment doctors are complicit in violating

human rights and exacerbating inequities and should be demanding more responsiveness from the state, including a uniform nationally accepted transparent rationing policy.[155]

As discussed in *Paper 5*, access to dialysis in the public sector in South Africa was famously tested in the constitutional courts in 1997.[157] The court upheld the decision to withhold dialysis in 41 year old man with diabetes and heart disease (i.e. he would not have been transplantable) citing that the state could not fulfill its' other constitutional health responsibilities should it provide dialysis for all, essentially valuing the utilitarian perspective above the rule of rescue as a matter of justice.[157] Ironically, had the patient belonged to a health insurance, the insurance may not legally have been able to deny him dialysis in the private sector.[155] The converse situation is also fraught with ethical challenges – if a dialysis patient in the public sector declines the offer of a kidney transplant they can be removed from dialysis (and allowed to die).[158] A recent ethical analysis argued that that this policy is defensible from a utilitarian perspective in trying to maximize the cost-effectiveness of RRT and achieve justice in terms of increasing the numbers of patients who can be accepted for dialysis because a slot is vacated when someone is transplanted.[158] Forcing a patient to undergo transplantation unwillingly does however severely compromise autonomy in terms of choice of treatment, although they still technically retain autonomy deciding whether to accept treatment and stay alive. Given that outcomes with transplantation are almost always superior to those on dialysis, this paternalistic policy could be argued to be in the patient's best interest and therefore adheres to the principle of beneficence.[158] The question of avoiding harm in this situation is more complex, however. A patient being pressured into transplantation may experience multiple harms, and the decision to remove a patient from dialysis as a consequence of refusal of transplantation directly hastens death. Harm to other patients, however, through a transplant-eligible patient remaining on dialysis and preventing others from having the opportunity to be dialyzed and transplanted must also be considered. Transparency and fully informed consent before initiation of dialysis is crucial to pre-emptively avoid this ethical quagmire.

Official rationing guidelines for access to dialysis do not exist in the rest of SSA beyond Sudan where dialysis quality is rationed (i.e. HD is provided twice instead of 3 times a week unless more is clinically indicated) in order to include more people (i.e. an egalitarian approach).[159] In several other countries local units are using the Western Cape guidelines with the belief that

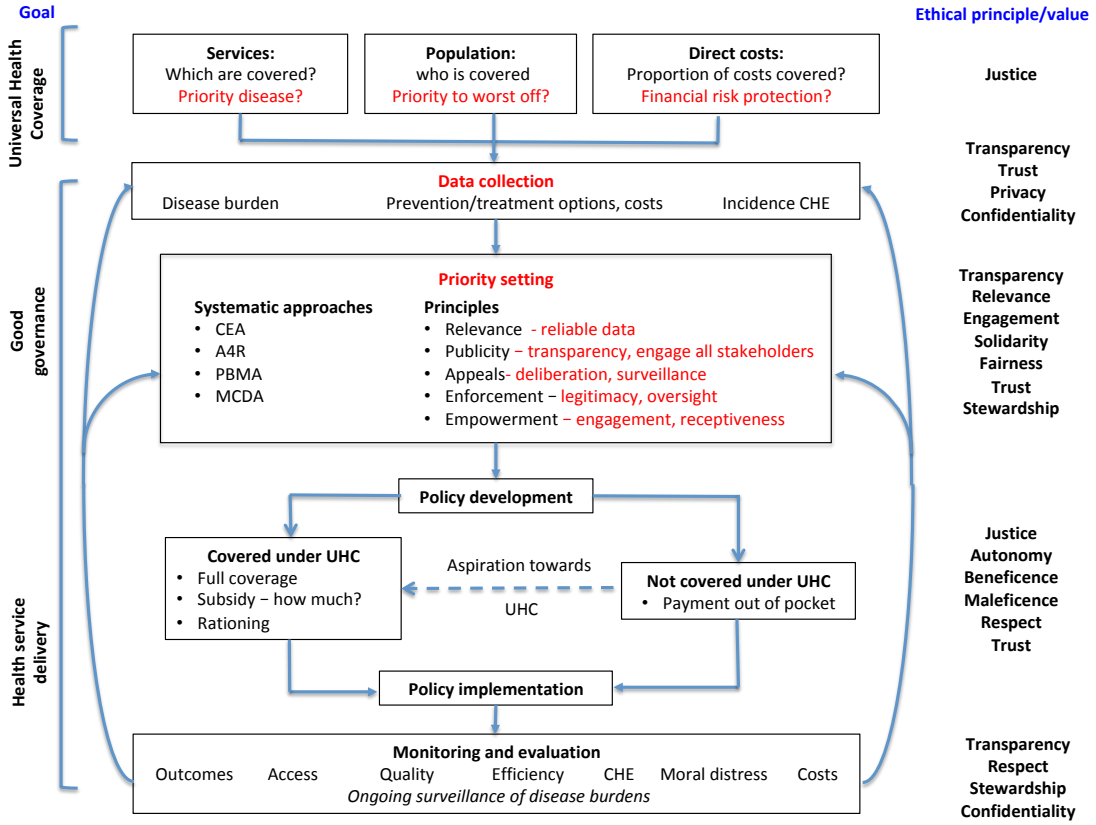
these are the more "ethical" criteria for patient selection. Ironically, however, in most of these settings transplantation is not an option at all, therefore justifying selection of patients on this basis seems problematic. "Transplantabilty" in these cases is presumed to be an indicator of a patient's likelihood to thrive on dialysis, however this would need to be tested locally. It is possible that this is not the case as the structural factors required to continue in-center HD, the only form of dialysis available in most SSA countries, are very different from those required to retain a functioning transplant.

Transparency of rationing criteria is therefore not enough to absolve stakeholders of moral obligations. Whenever rationing is considered or practiced, there should be a commitment to progressive lowering of barriers to care such that over time more people have access to the care they need.[160] In addition, if life-saving treatment such as dialysis is to be rationed, the responsibility of this decision implies provision of an alternative – compassionate supportive care for the patient and family until death ensues. This level of care is also often lacking in SSA.

CONCLUSIONS AND PERSONAL REFLECTIONS

The ethical challenges raised by kidney disease and the realities of its treatment in SSA and other resource limited settings are many, and cut across multiple levels of society and the health system. Good health systems governance is required to measure and acknowledge the burden of kidney disease in terms of numbers, moral distress and CHE, in terms of priority setting and resource allocation, in terms of progressive realization of UHC and the right to health, and in terms of transparent policy development regarding access to high cost care when resources are limited. Communities must be well informed and health care workers must be well trained and supported. All stakeholders must be willing to engage in the policy process and in holding governments and each other accountable for practice and progress. The continuum of this process from the health systems perspective is illustrated in Figure 6. Each stage originates from population health needs and is associated with ethical values or principles which necessitate effective engagement with all relevant stakeholders. Once policies are developed and implemented, good oversight is crucial to ensure accountability and to provide iterative feedback and adaptation such that the goals of UHC may be progressively approached.

Figure 6: Schematic diagram of policy development and priority setting from the health systems perspective



PBMA – Programme budgeting and marginal analysis; CEA – cost-effectiveness analysis; A4R – Accountability for Reasonableness; MCDA – multi-criteria decision analysis.

At present, in addition to illness itself, there is much harm associated with developing kidney failure in SSA: access to life-saving dialysis is highly inequitable and not accessible to the less privileged in society; dialysis quality when obtained may be suboptimal because of infrastructural barriers, insufficiently trained staff, patient and/or institutional cost constraints; CHE is frequent; mortality is high; moral distress of health care workers is frequent. Patient autonomy appears a relative luxury under current circumstances. The benefits of dialysis are primarily limited to those who can continue to pay and survive, to those who make a profit from dialysis (industry and fee-for-service practitioners/institutions), and to enhancement of institutional reputations. Rationing of dialysis is happening either explicitly or implicitly on a daily basis. A major ethical challenge is how to develop transparent, appropriate and just local guidance to enhance equitable access to such a high-cost, necessarily limited, resource.

The daily dilemma of the health care worker is well illustrated by Syrett[161] who describes the analogy of a physician who is so busy jumping in and pulling drowning people out of a river as they rapidly float past that he/she has no time to consider why they are all falling in in the first place. In doing this PhD I have tried to look upstream and understand why people are falling into the river. I realize that at the river's source are all the "causes of the causes" of ill health in SSA which reach back into the history of past centuries and are still very prevalent today.[162] Because of these factors many people do not learn to swim. There are no barriers along the river and therefore some people fall in. Some were already wearing a lifejacket, others are strong enough to soon pull themselves ashore, the weaker ones are swept away. Some are thrown a life jacket and are pulled out along the way, others become exhausted trying to stay afloat. Some drown and some are pulled out by the physician downstream, at times they can be resuscitated, at times not. The physician cannot stop, but feels demoralized.

If one looks at this story through an ethical lens, on the face of it, it seems less a problem of ethics than a problem of coping with reality. However, governments are obligated to make it possible for people to be educated about the dangers of the river, to be able and strong enough to swim and ideally to have their own life jacket. This is not happening as fast as it should therefore there is an ethical imperative for this process to speed up and be comprehensive. An urgent ethical challenge arises when there are not enough life jackets, to whom should they be thrown? Which of the drowning people does the physician try to rescue first? Should the government erect a safety net downstream to catch people? Is simply pulling people out of the water enough? Where does the physician's role start and end?

I have argued here that having transparent guidelines in place for both priority setting and rationing, to guide consistent and equitable policy development and implementation should make it easier for all stakeholders and in effect "insulate" individuals from having to make *ad hoc* decisions on access to dialysis. From a nephrologist's perspective, this is true to a large extent, and may be the most pragmatic solution available at present, but this does not change the fact that care will still be denied to some patients in need. As illustrated by the tension within South Africa about the category 2 patients, many patients will fall into grey areas and strict application of any rationing criteria will not be simple. Nephrologists also cannot simply ignore that kidney disease is often a result of, or at least is exacerbated by, many social and

structural factors, that if left unremedied will continue to increase the burden of disease. Advocating for equitable care just at the end of the line when a patient has reached a life-or-death crisis is not enough.

Social disadvantage and NCDs such as kidney disease are mutually enforcing.[163] Chronic disease itself, especially dialysis, significantly impacts how patients can cope with disease.[164] Nephrologists in most settings are in a position to witness the impact of structural violence on patients' lives, and as such have an ethical obligation to raise awareness and advocate for a holistic and more primordial approach to optimizing health and maximizing individual capabilities to thrive.[165-167] Physicians must reflect on their role, how they can contribute and what they are comfortable to engage with.[147] It is becoming increasingly difficult in all countries to shy away from the reality that rationing is happening. Physicians and other health care workers at the bedside are best placed to try to impact how this happens, to optimize equity and transparency.

When I used to advocate for my dialysis patients in South Africa as a young nephrologist I always had a niggling feeling in the back of my mind that if I was successful some other programme would not get what they asked for. On some level I felt it was the responsibility of others to advocate for their own patients, but increasingly I realized that it was also the responsibility of the hospital chief executive officer to determine where the limited resources might be best allocated. Having been more exposed to the arena of public health in the past few years, my view point has been broadened to understand that striving for distributive justice is key in health care decision making, however the tension between the bedside and the boardroom will always exist. Three common values, described in a study of 20 Australian public health physicians strongly resonate with me: "personal ethics" (being responsible, persistent, loyal to cause), "justice" (striving for distributive justice and equity, trusting institutions) and "practices of augmentation" (generating evidence, being moderate).[168] The authors concluded that these values were consistent with the 3 levels of "little ethics" put forward by Paul Ricoeur: "(aiming for a) 'good life', with and for others, in just institutions". Just institutions are fundamental to progress in health care and as such, physician advocates can play a role in highlighting inequities and holding governments and other stakeholders accountable. The South African constitutional court, in upholding the dialysis rationing decision in 1997, included a caveat, that there was an

obligation on the state to progressively aim to realize the right to dialysis for all.[110] Although still an aspiration, this statement underscores the need for rationing when resources are limited, but also that it is at best an uncomfortable compromise. Complacency with the status quo is unacceptable. Ultimately, "good health cannot be assured to everyone. But good health *care* can and should be guaranteed."[169]

Future directions

The work presented in this thesis paints the picture of prevalent inequities in access to care for kidney disease and dialysis in SSA. The added complexities of access to transplantation in SSA must be further explored. The nephrology community is calling for access to dialysis for AKI as a human right. The concept of health as a human right and how far state obligations should extend regarding access to unaffordable high-cost interventions requires further deliberation. Priority setting and rationing may be part of the solutions, but other stakeholders must be engaged and held accountable as well. The global dialysis market was valued at USD 75 billion in 2011.[170] It has grown significantly since then. Individual company profits reach the billion range annually.[171,172] Dialysis companies have not been held accountable for their high pricing and lack of transparency. The ethical obligations of such market giants will be explored in the context of recent calls for fair profits and fair pricing from institutions such as the WHO. The role of private health care in resource-limited settings is necessary but ethically complex. Public-private partnerships are being promoted as a sustainable way forward in low resource settings. Work towards the development of some broad ethical guidelines is required. Professional societies are pushing for expansion of dialysis practice in low-income settings and are embarking on interventions without being embedded in the local health system. As such, despite good intentions, in the bigger picture, more harm may be being done than good. The ethical principles applying to implementation research must be applied in planning such "humanitarian" interventions even when not labeled research. These concepts must be brought into the mainstream to ensure responsiveness, consistency, transparency and sustainability. Future work will also focus on building capacity among nephrologists and other health care workers in low-income settings to enable identification and articulation of the ethical challenges in their daily work, to cope with moral distress and to support effective advocacy for equitable decision-making in their environments.

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